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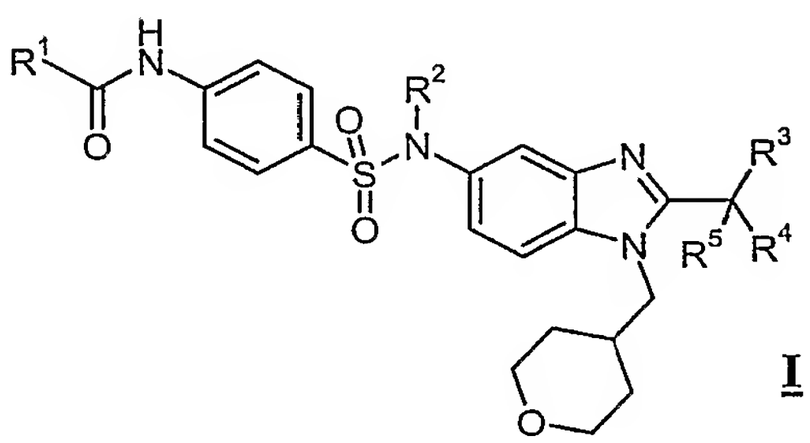
(54) Title: Benzimidazole derivatives and their use as cannabinoid receptor ligands

(57) Abstract: Compounds of Formula I, or pharmaceutically acceptable salts thereof: (I) wherein R^1, R^2, R^3, R^4, and R^5 are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.



I

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Benzimidazole derivatives and their use as cannabinoid receptor ligands

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB_1 receptor, CB_2 receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB_1 receptor agonists, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB_1 receptors located in CNS. There are lines of evidence, however, suggesting that CB_1 agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB_1 receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB_1 receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-6}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

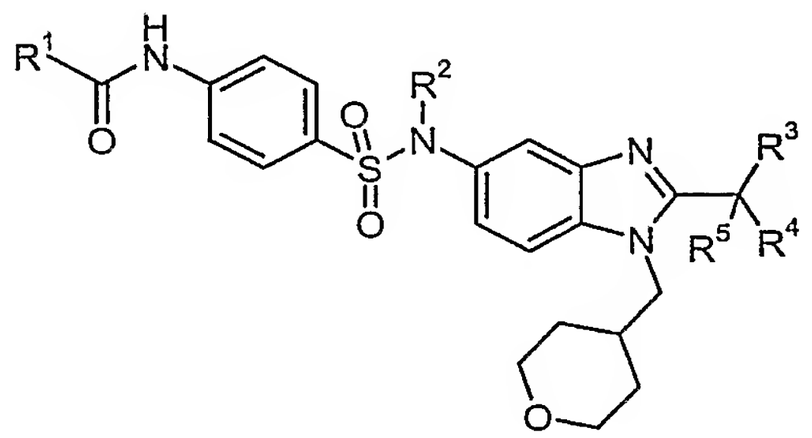
The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 2 to 5 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C_{2-5}heterocycloalkyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl, and C_{3-6}cycloalkyl are optionally substituted by one or more groups selected from amino, cyano, halogen, and C_{2-5}heterocycloalkyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

Another embodiment of the invention provides a compound of formula I, wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

Another embodiment of the invention provides a compound of formula I, wherein

R^1 is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl;

R^2 isselected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

A further embodiment of the invention provides a compound of formula I, wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are methyl.

A further embodiment of the invention provides a compound of formula I, wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 is selected from –H and methyl;

R^3 is methyl; and

R^4 and R^5 are fluoro.

An even further embodiment of the invention provides a compound of formula I,

wherein

R^1 is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are methyl.

A yet even further embodiment of the invention provides a compound of formula I,

wherein

R^1 is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl;

R^2 is selected from –H and methyl;

R^3 is methyl; and

R^4 and R^5 are fluoro.

A yet even further embodiment of the invention provides a compound of formula I,

wherein

R^1 is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl;

R^2 is –H; and

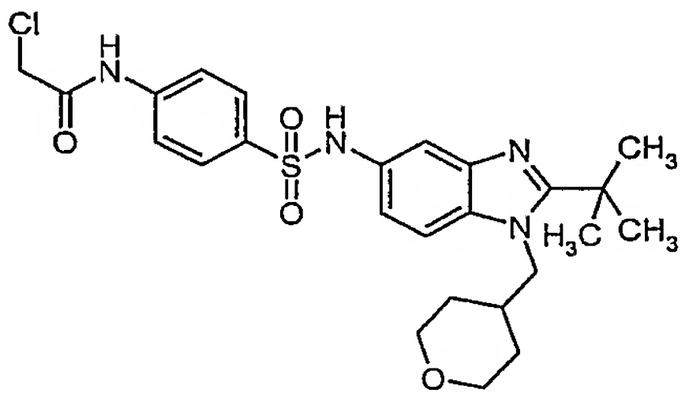
R^3, R^4 and R^5 are methyl.

In another embodiment, R^1 of formula I is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl.

In another embodiment, R^2 is selected from –H and methyl.

In another embodiment, R^3, R^4 and R^5 are independently selected from fluoro and methyl.

A further embodiment of the invention provides a compound selected from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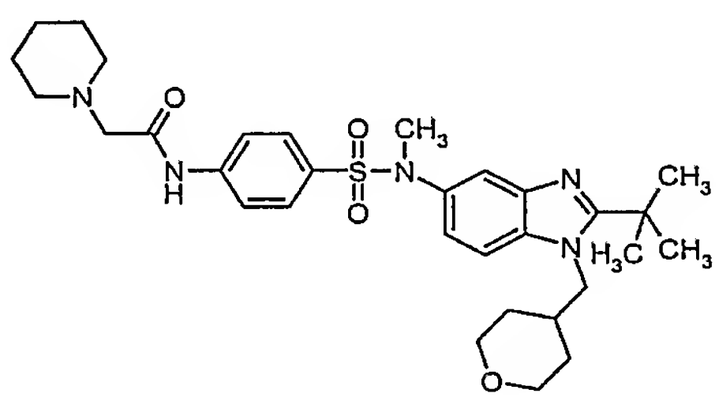
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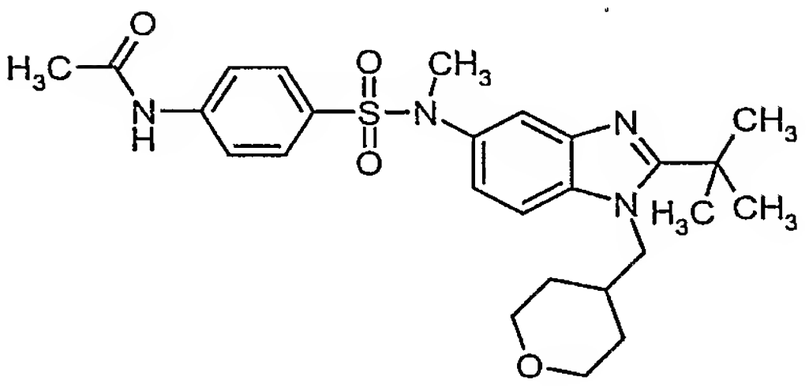
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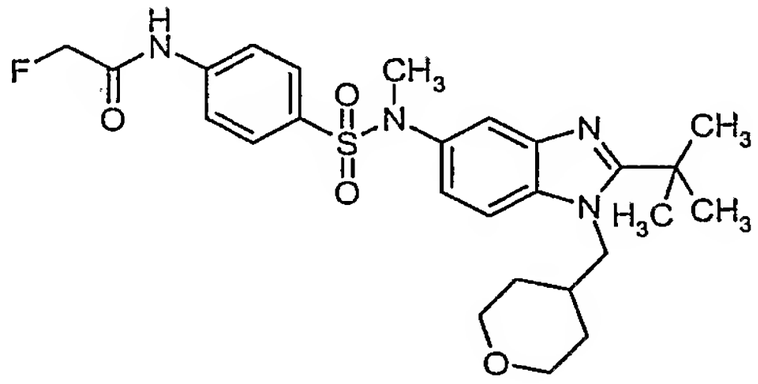
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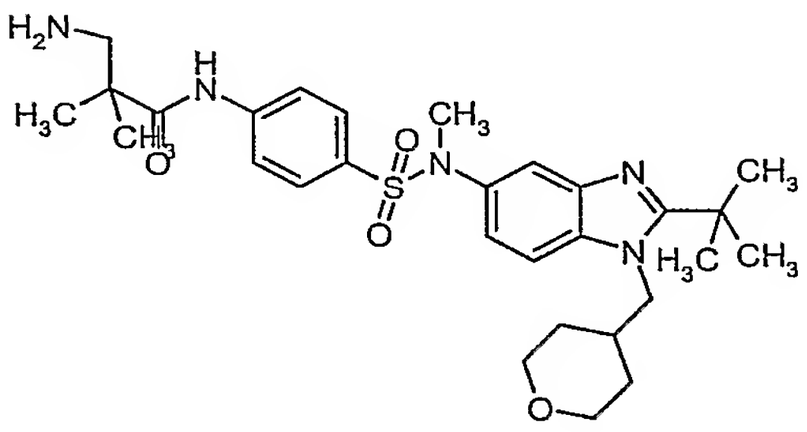
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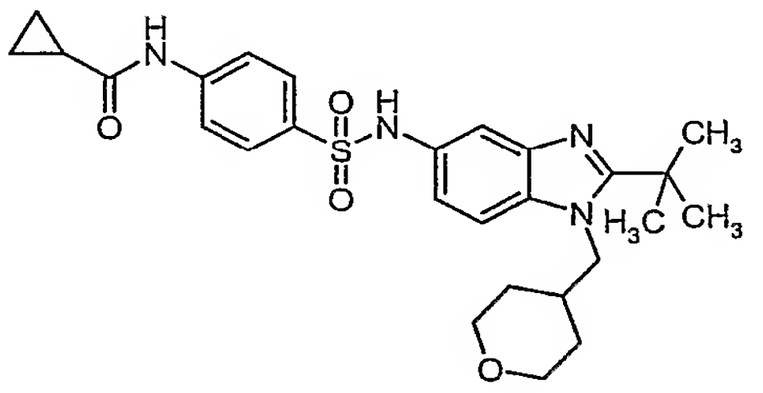
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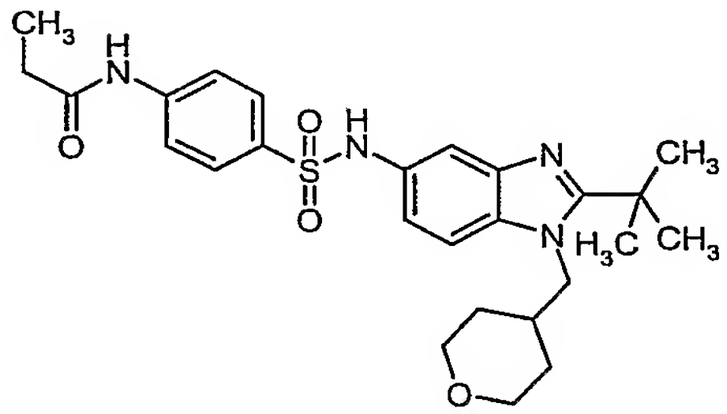
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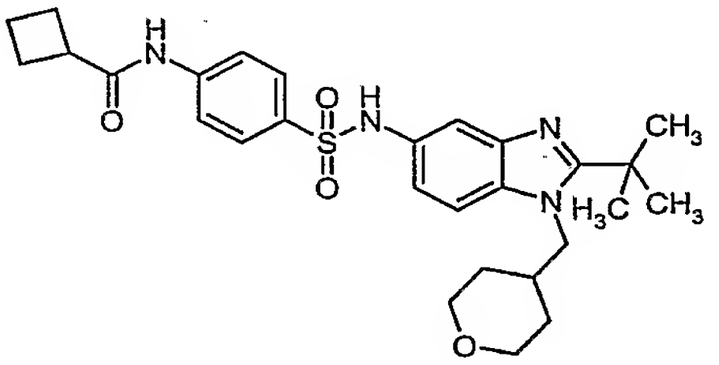
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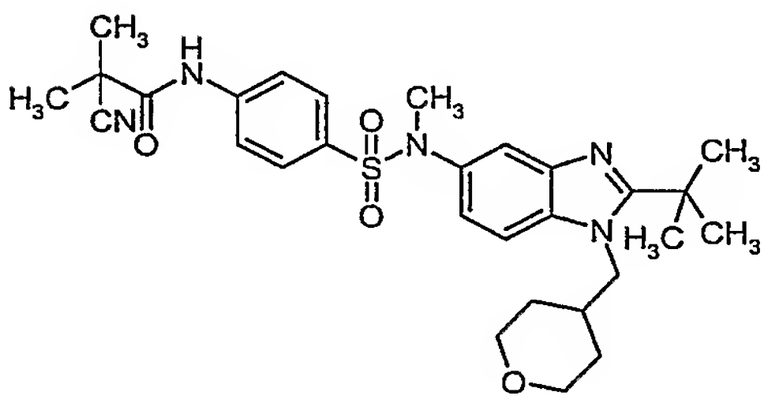
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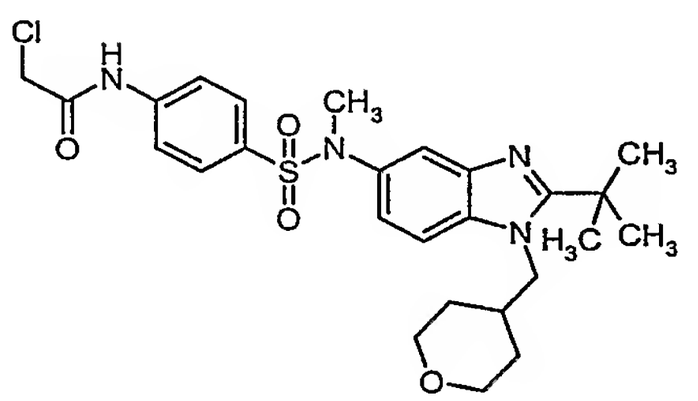
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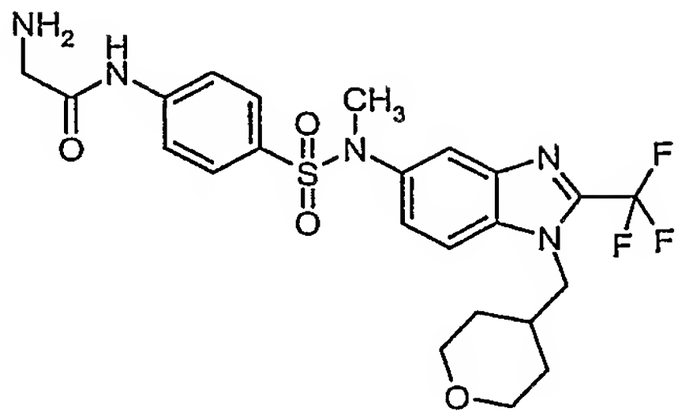
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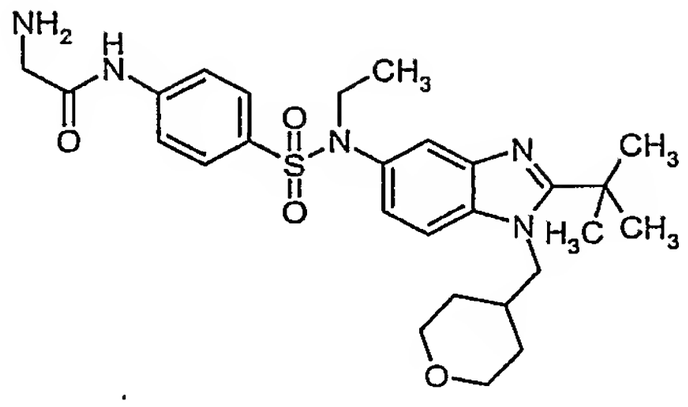
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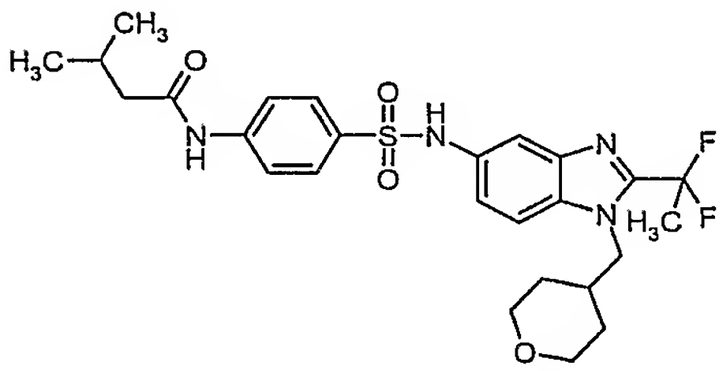
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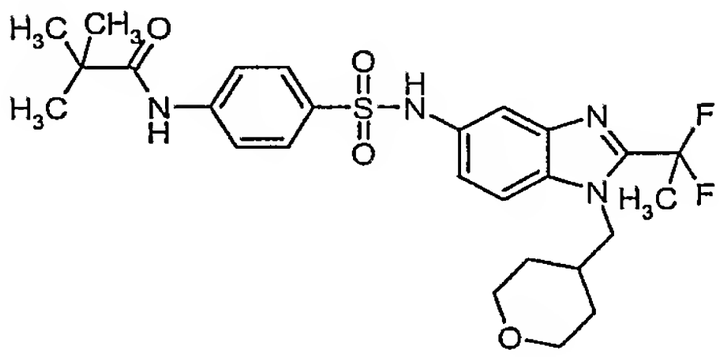
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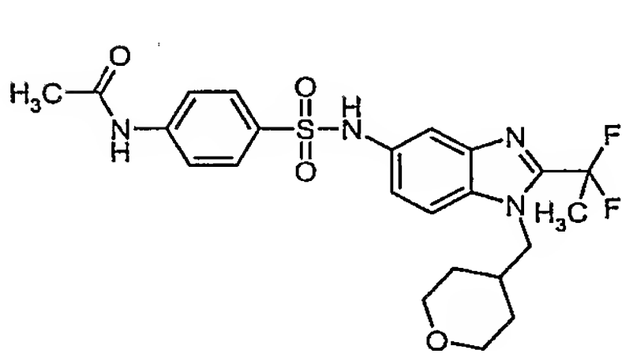
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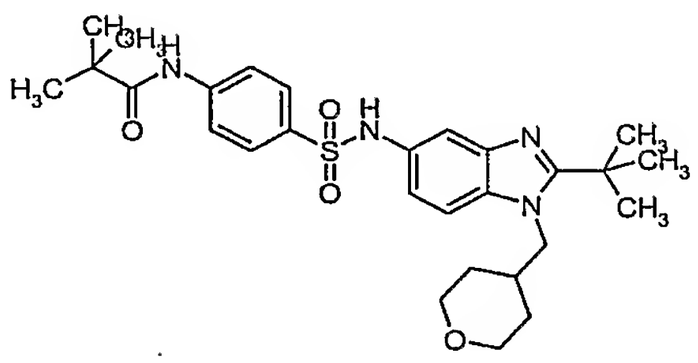
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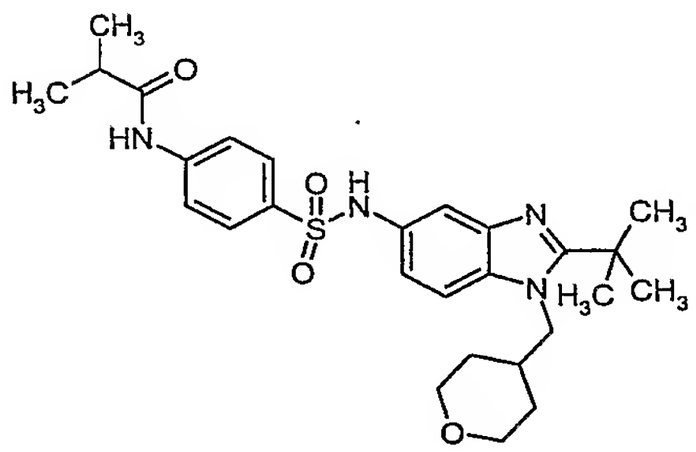
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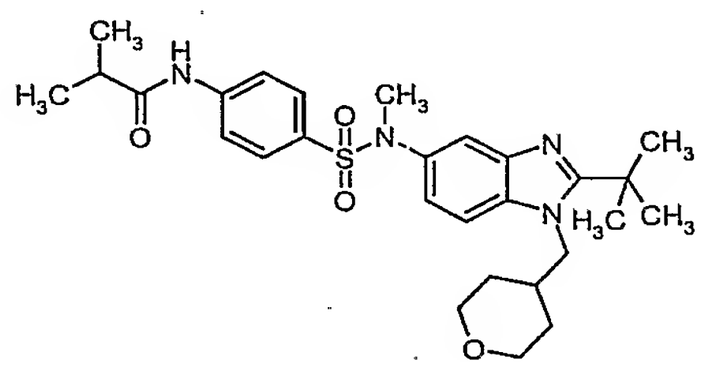
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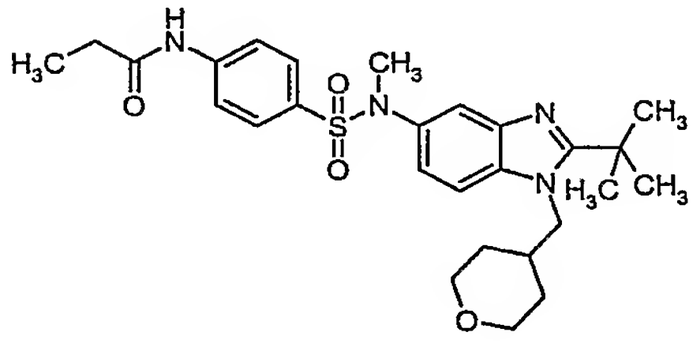
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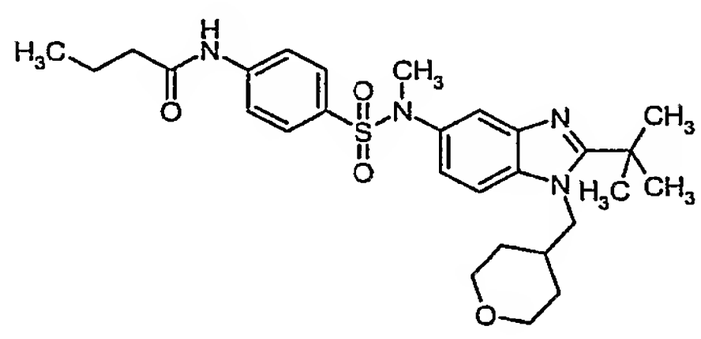
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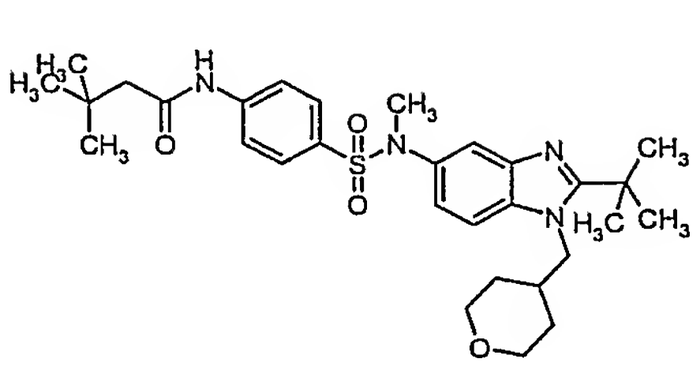
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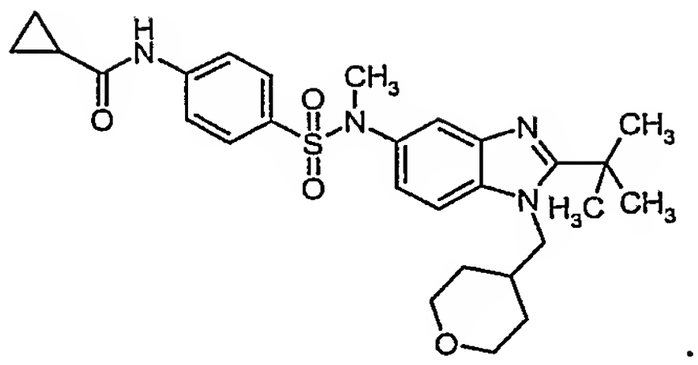
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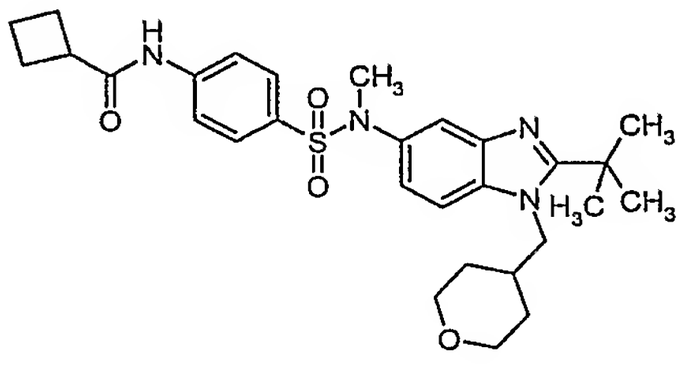

, and pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium,

potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB_1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress

disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson´s disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This

definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

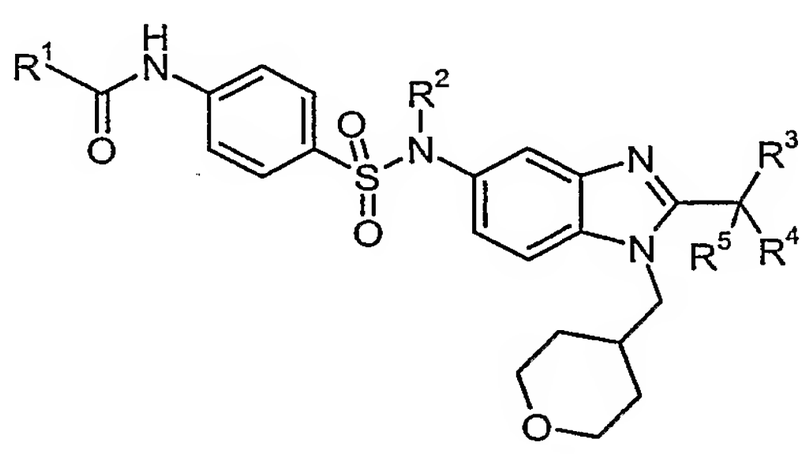
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

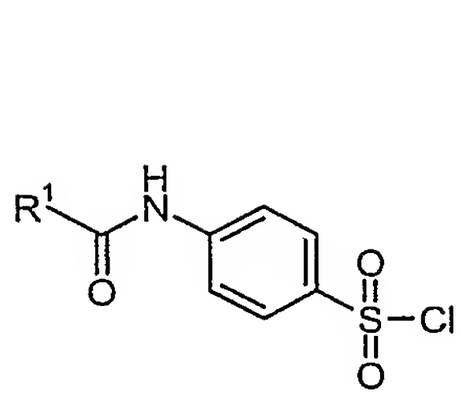
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula I, comprising:

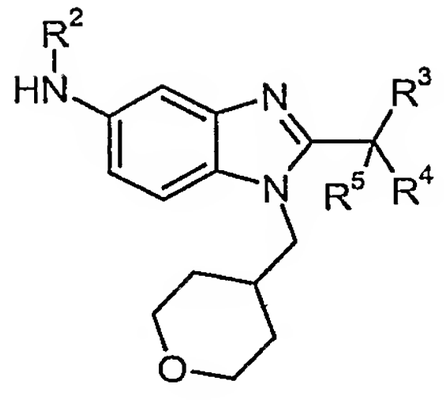


I

reacting a compound of Formula II with a compound of formula III,



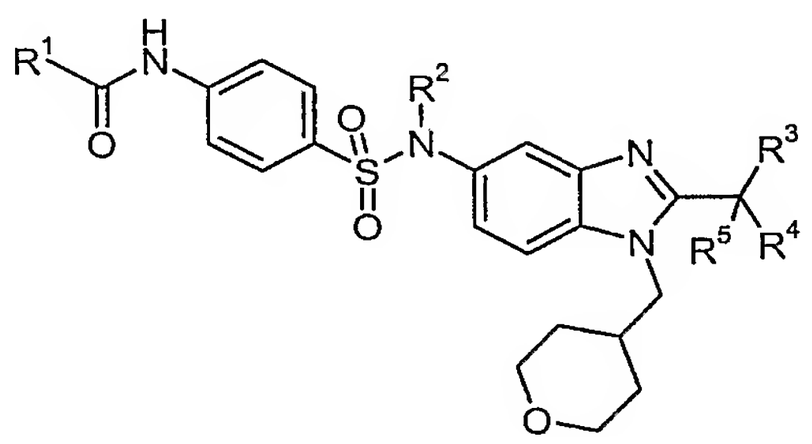
II



III

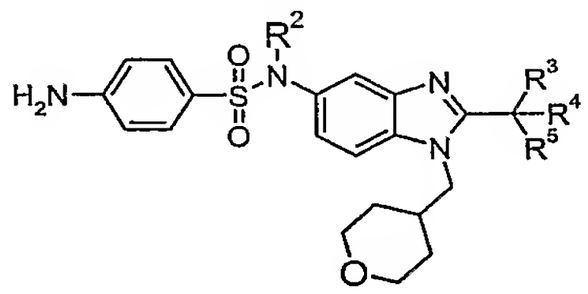
wherein R^1, R^2, R^3, R^4 and R^5 are as defined above.

In another embodiment, the invention provides a process for preparing a compound of Formula I, comprising



I

reacting a compound of Formula IV with R^1-C(=O)-X,

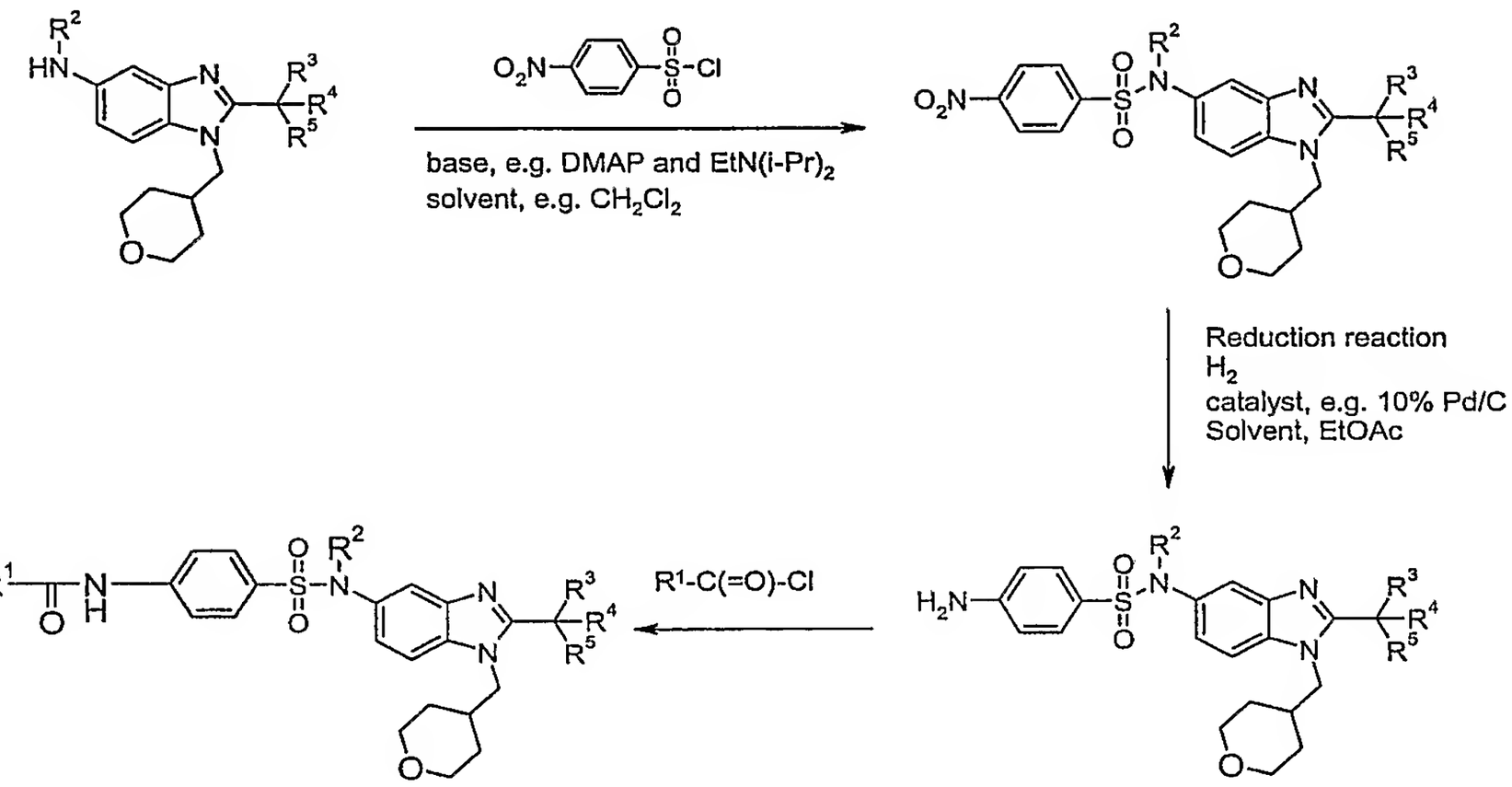


IV

wherein R^1, R^2, R^3, R^4 and R^5 are as defined above; and X is selected from -Cl, -Br and -I.

Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Scheme 1.

Scheme 1



R1, R2, R3, R4 and R5 are as defined above.

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor from BioSignal (hCB_2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB$_1$ and hCB$_2$ GTPγS binding

Human CB$_1$ receptor from Receptor Biology (hCB$_1$) or human CB$_2$ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The EC_{50} and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPg^{35}S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB$_2$) or 10 µM (hCB$_1$) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB2) or 112.5 µM (hCB$_1$) GDP prior to distribution in plates (15 µM (hCB$_2$) or 30 µM (hCB$_1$) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$Ki = IC_{50}/(1+[rad]/Kd)$,

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

Using the above-mentioned assays, the Ki towards human CB$_1$ receptors for certain compounds of the invention are in the range of between 2.8 nM and 1846 nM.

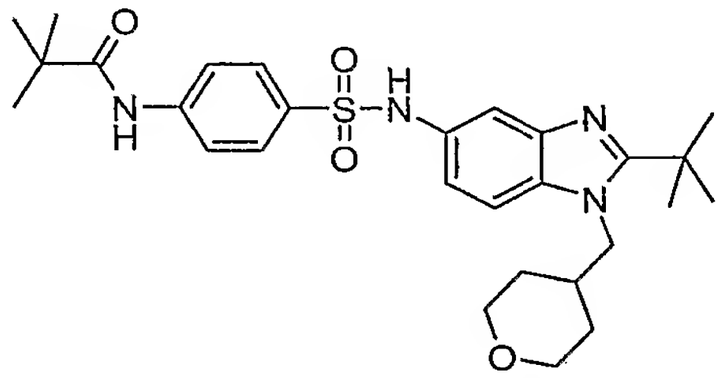
EC_{50} for these compounds are in the range of between 1.8 nM and 682 nM. Emax for these compounds are in the range of between 78% and 157%.

EXAMPLES

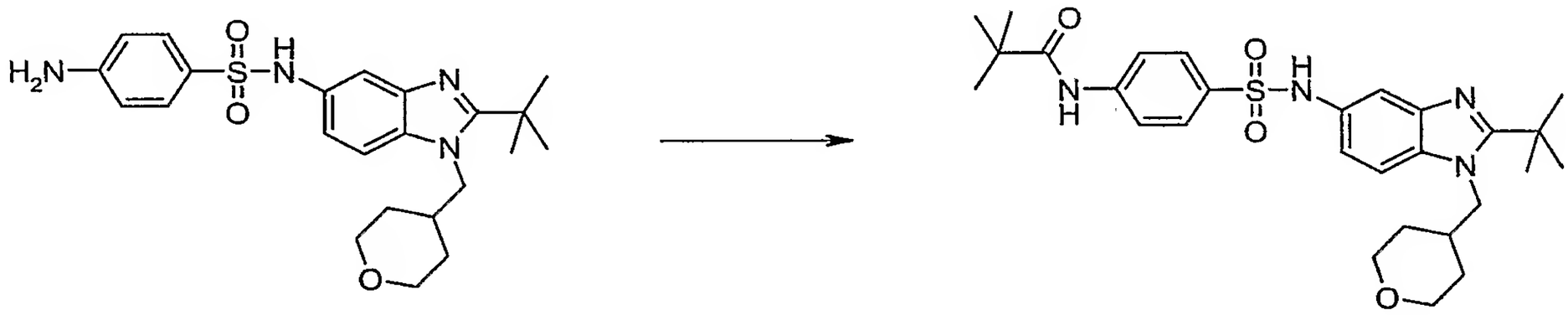
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2,2-dimethylpropanamide**



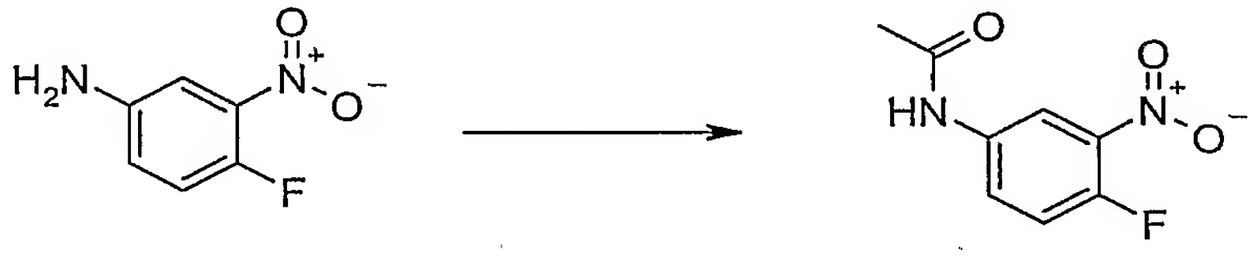
Step A: *N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2,2-dimethylpropanamide



Trimethylacetyl chloride (41 uL, 40.0mg, 0.33 mmol) was added to a solution of DMAP (51.0 mg, 0.42 mmol) and 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (see following Steps B, C, D, E, F, G and H for preparation) (75.2 mg, 0.17 mmol) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 6 at rt, quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with CH_2Cl_2 (3x5 mL). The combined organic phases were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The product was

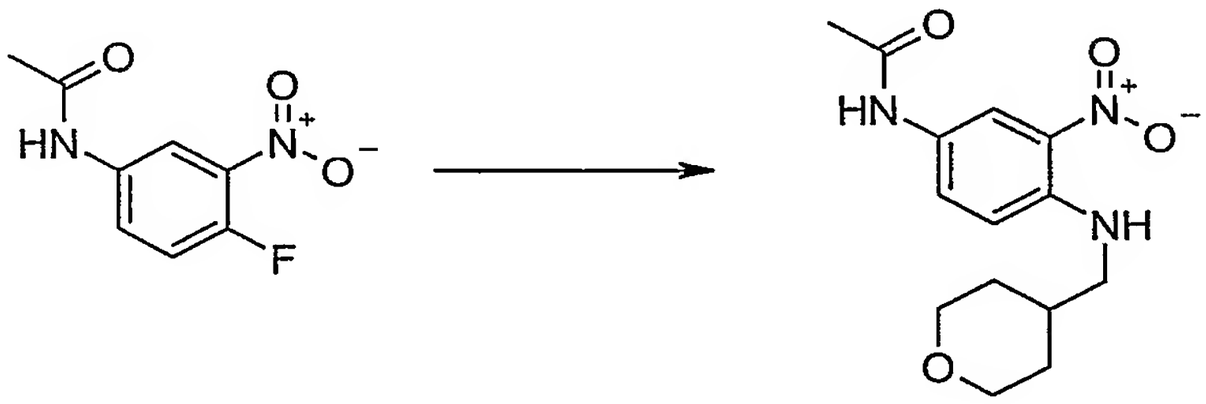
purified by silica gel flash chromatography using EtOAc as eluent. Yield: 78.5 mg (87%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.25 (s, 9 H), 1.43 - 1.59 (m, 4 H), 1.64 (s, 9 H), 2.23 - 2.40 (m, 1 H), 3.29 - 3.39 (m, 2 H), 3.86 - 3.98 (m, 2 H), 4.45 (d, J=7.42 Hz, 2 H), 7.25 (dd, J=8.83, 1.41 Hz, 1 H), 7.61 (s, 1 H), 7.71 (s, 4 H), 7.79 (d, J=8.96 Hz, 1 H). MS (ESI) $(M+H)^+$ = 527.0. Anal. Calcd for $C_{28}H_{38}N_4O_4S$+1.50 HCl+0.40 H_2O (588.60): C, 57.14; H, 6.90; N, 9.52; Found: C, 57.11; H, 6.91; N, 9.42.

Step B: *N*-(4-Fluoro-3-nitrophenyl)acetamide



4-Fluoro-3-nitroaniline (5.0g, 32.0 mmol) was dissolved in 50 mL of DCM at 0°C containing TEA (6.7 mL, 48.0 mmol). Acetyl chloride (2.75 mL, 38.4 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was crystallized from DCM. Yield: 5.3g (84%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 2.04 (s, 3 H), 7.51 (dd, J=11.23, 9.08 Hz, 1 H), 7.80 (ddd, J=9.08, 4.00, 2.93 Hz, 1 H), 8.47 (dd, J=7.03, 2.73 Hz, 1 H), 10.38 (s, 1 H).

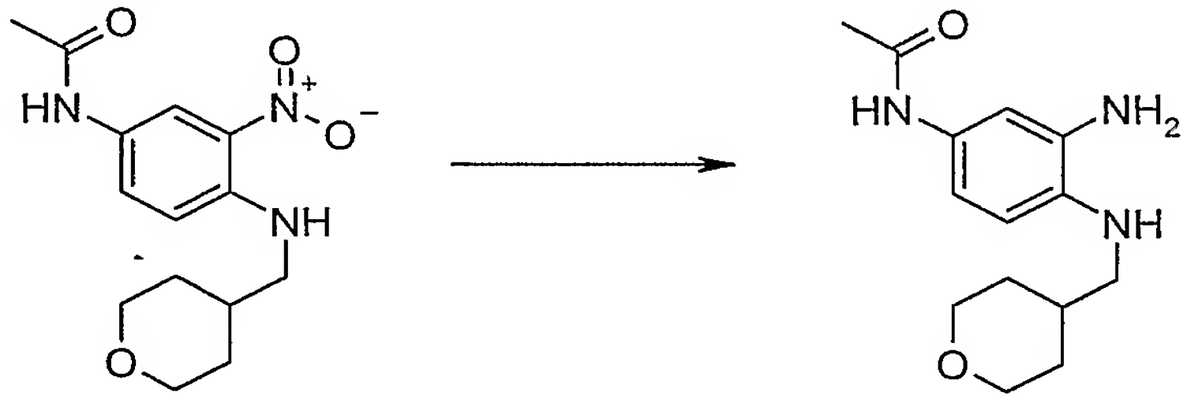
Step C: *N*-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



N-(4-Fluoro-3-nitrophenyl)acetamide (500 mg, 2.52 mmol) and 4-aminomethyl tetrahydropyran (350 mg, 3.02 mmol) were stirred in 20 mL of EtOH containing TEA (0.525 mL, 3.78 mmol) at 75°C overnight. The solvent was concentrated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated

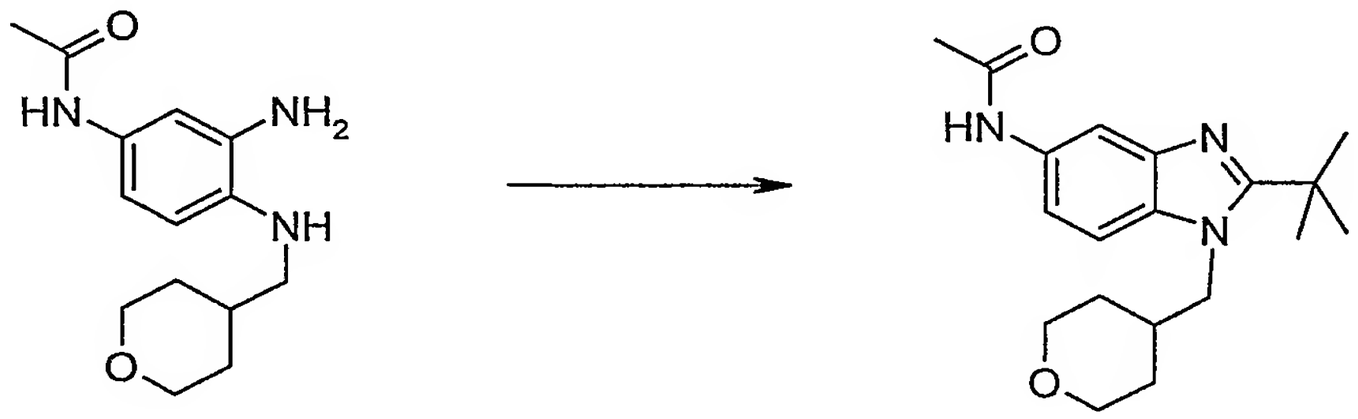
aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 611 mg (83%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (m, 2 H), 1.74 (m, 2 H), 1.89 – 2.00 (m, 1H), 2.18 (s, 3 H), 3.22 (dd, J=6.44, 5.66 Hz, 2 H), 3.42 (m, 2 H), 4.02 (m, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 – 8.12 (m, 1 H).

Step D: *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



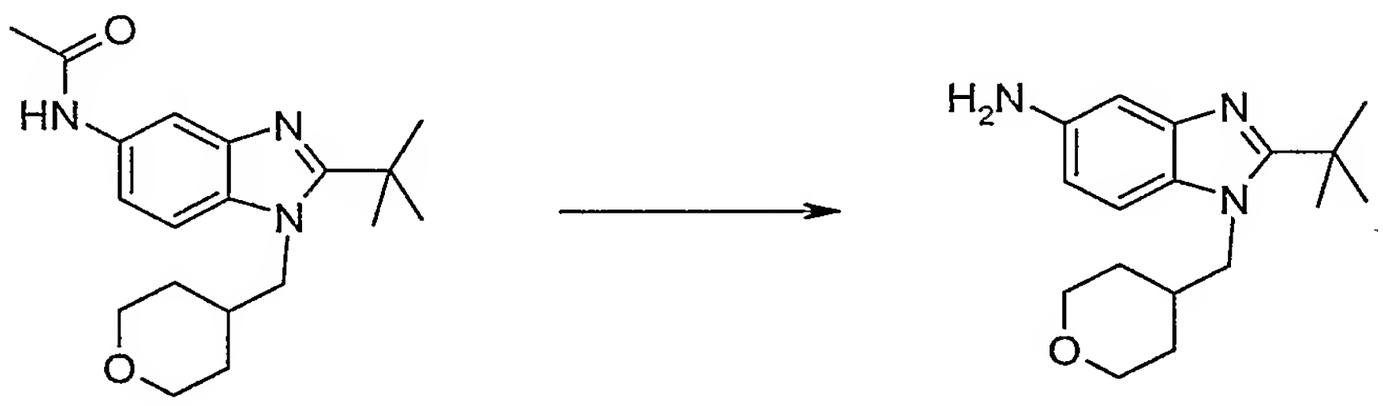
N-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (605mg, 2.06 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 315mg (58%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (m, 2 H), 1.74 (m, 2 H), 1.82 – 1.91 (m, 1H), 2.13 (s, 3 H), 2.99 (d, J=6.64, 2 H), 3.42 (m, 2 H), 4.02 (dd, J=10.94, 3.71 Hz, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 – 8.12 (m, 1 H).

Step E: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



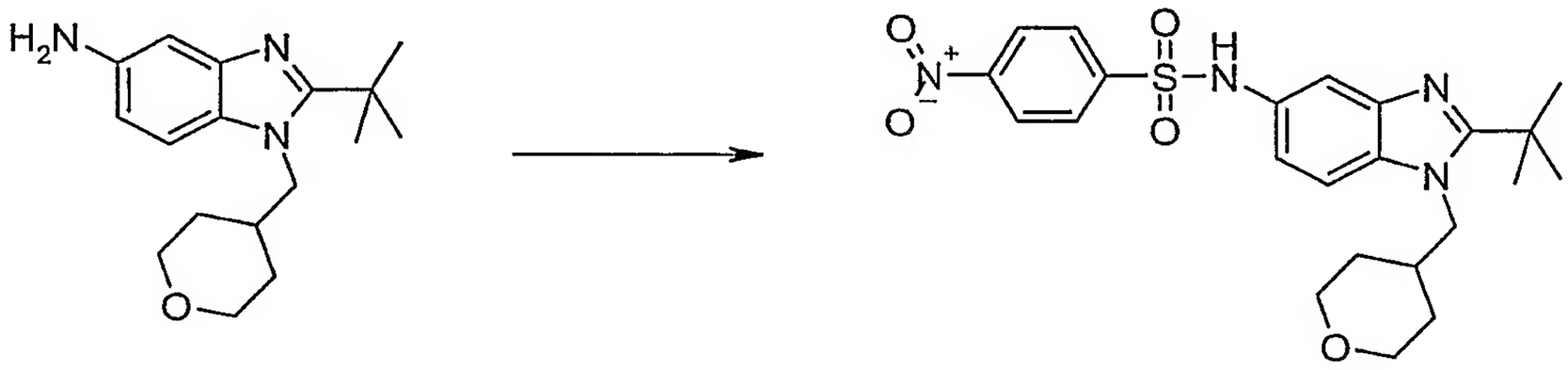
N-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (315 mg, 1.20 mmol) and DMAP (30 mg, 0.240 mmol) were dissolved in 20 mL of DCM. Trimethylacetyl chloride (0.160 mL, 1.32 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 3 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : acetone as eluent. Yield: 135 mg (34%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.48 – 1.54 (m, 4 H), 1.56 (s, 9 H), 2.20 (s, 3 H), 2.24 – 2.35 (m, 1 H), 3.28 – 3.35 (m, 2 H), 3.96 (t, J= 2.83 Hz, 1 H), 3.99 (t, J= 3.03 Hz, 1 H), 4.19 (d, J=7.42 Hz, 2 H), 7.27 (d, J=8.59 Hz, 1 H), 7.34 (br.s, 1 H), 7.57 (dd, J=8.79, 1.95 Hz, 1 H), 7.67 (d, J=1.95 Hz, 1 H).

Step F: 2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



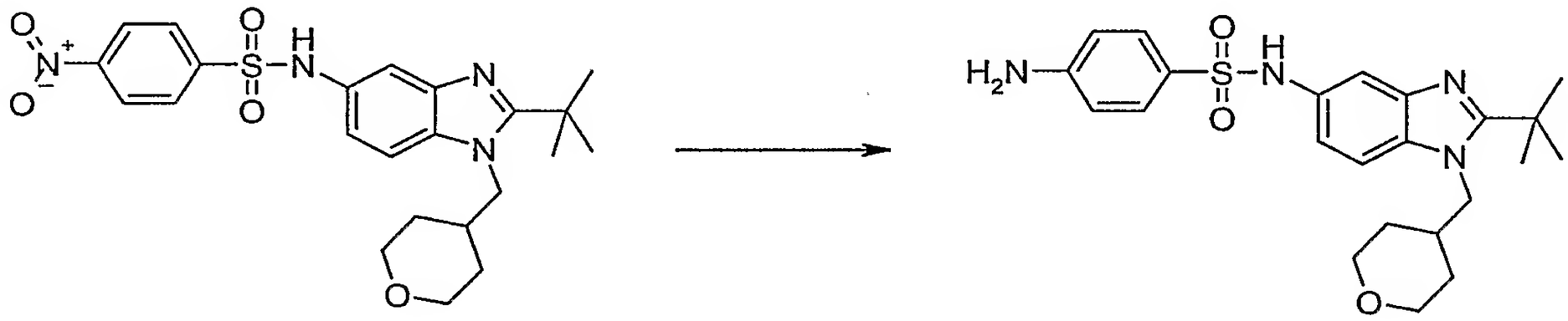
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (135 mg, 0.409 mmol) was dissolved in 4 mL of 1:1 / EtOH:2M HCl. The solution was heated at 120°C for 30 min using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with 2M NaOH solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 117 mg (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.47 – 1.52 (m, 4 H), 1.54 (s, 9 H), 2.23 – 2.31 (m, 1 H), 3.28 – 3.36 (m, 2 H), 3.96 (t, J= 3.12 Hz, 1 H), 3.97 – 4.00 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 6.66 (dd, J=8.40, 2.15 Hz, 1 H), 7.06 (d, J=2.15 Hz, 1 H), 7.10 (d, J=8.40 Hz, 1 H).

Step G: *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide



2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (94.3 mg, 0.328 mmol) and 4-nitrobenzenesulfonyl chloride (88.8 mg, 0.361 mmol) were stirred in 5 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 124.8 mg (81%). MS (ESI) $(M+H)^+$ = 473.07.

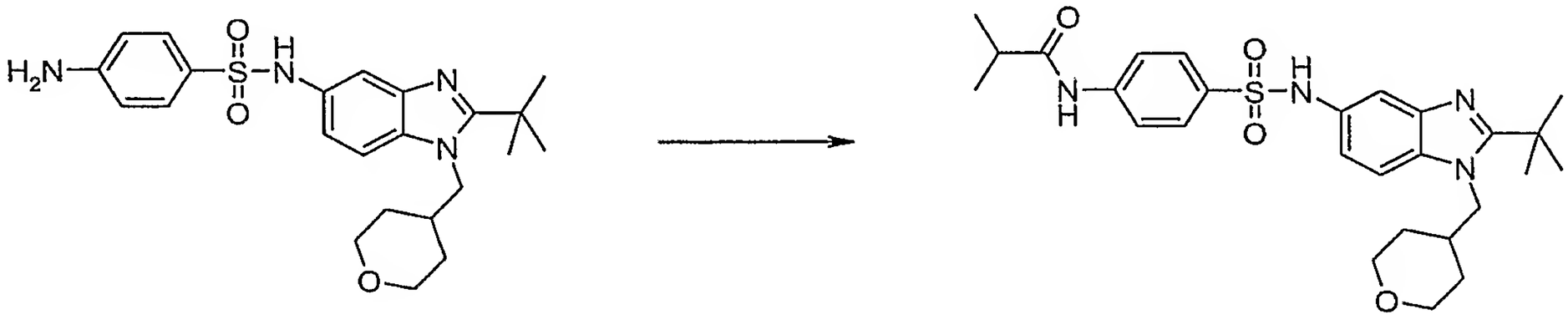
Step H: 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide (124.8 mg, 0.264 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 116.9 mg (99%). MS (ESI) $(M+H)^+$=443.08.

Example 2

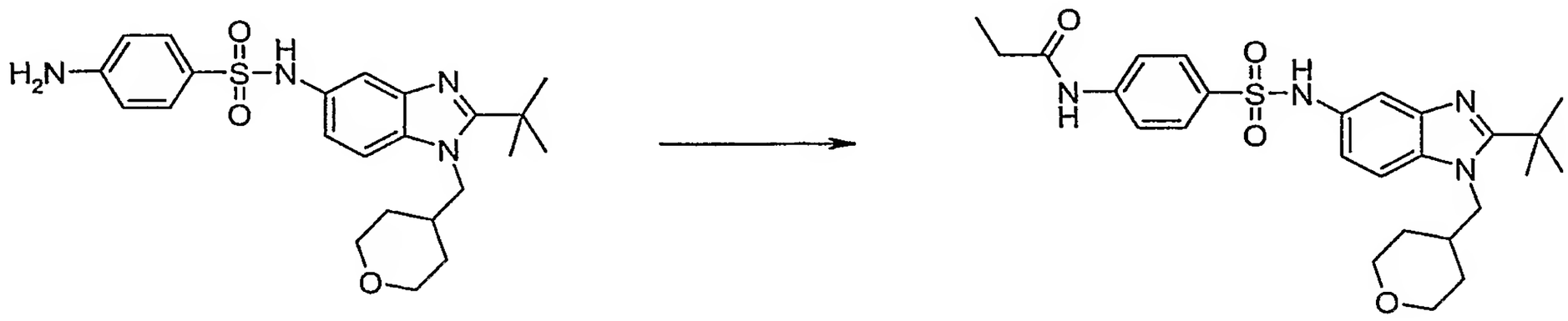
***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2-methylpropanamide**



Following the procedure for Step 1 in Example 1, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (40.3 mg, 0.091 mmol), isobutyryl chloride (21 uL, 21.3 mg, 0.20 mmol) and DMAP (30.5 mg, 0.25 mmol) in 5 mL of in DCM. The product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 17.6 mg (31%); ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.15 (d, J=6.91 Hz, 6 H), 1.40 - 1.54 (m, 4 H), 1.56 (s, 9 H), 2.23 - 2.36 (m, 1 H), 2.53 - 2.63 (m, 1 H), 3.31 - 3.35 (m, 2 H), 3.86 - 3.96 (m, 2 H), 4.32 (d, J=7.42 Hz, 2 H), 7.10 (dd, J=8.70, 1.79 Hz, 1 H), 7.40 (s, 1 H), 7.54 (d, J=8.71 Hz, 1 H), 7.63 - 7.67 (m, 4 H); MS (ESI) $(M+H)^+ = 513.0$; Anal. Calcd for $C_{27}H_{36}N_4O_4S$+0.90 TFA+0.90 H_2O +0.30 MeOH(641.12): C, 54.52; H, 6.27; N, 8.74; Found: C, 54.52; H, 6.29; N, 8.74.

Example 3

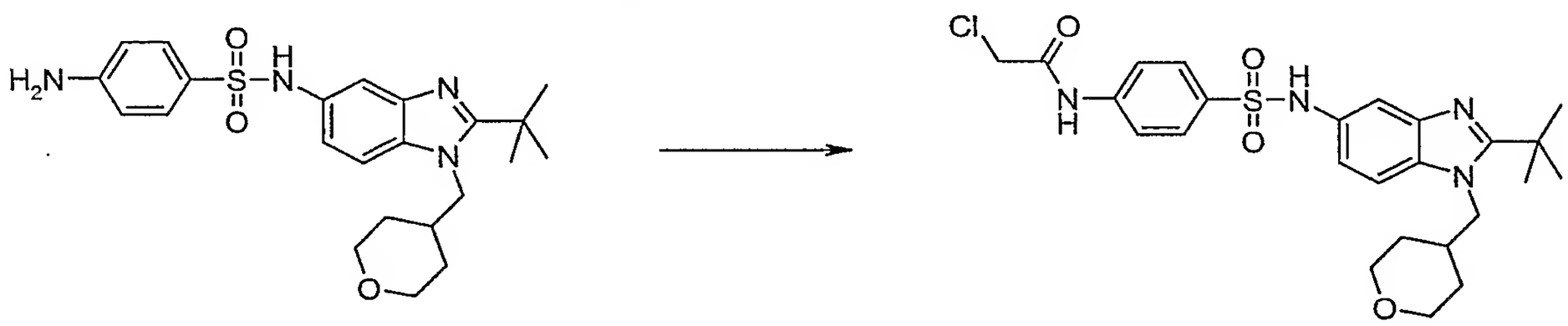
***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]propanamide**



Following the procedure for Step 1 in Example 1, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (61.8 mg, 0.14 mmol), propionyl chloride (15 uL, 15.9 mg, 0.17 mmol) and DIPEA (39.7 mg, 0.30 mmol) in 10 mL of in DCM. The product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 30.3 mg (35%); ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.15 (t, J=7.68 Hz, 3 H), 1.45 - 1.59 (m, 4 H), 1.64 (s, 9 H), 2.26 - 2.33 (m, 1 H), 2.37 (q, J=7.42 Hz, 2 H), 3.30 - 3.37 (m, 2 H), 3.90 - 3.93 (m, 2 H), 4.45 (d, J=7.42 Hz, 2 H), 7.24 (dd, J=8.96, 2.05 Hz, 1 H), 7.61 (d, J=1.79 Hz, 1 H), 7.64 - 7.67 (m, 2 H), 7.68 - 7.73 (m, 2 H), 7.79 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+ = 499.0$; Anal. Calcd for $C_{26}H_{34}N_4O_4S$+1.40 TFA+ 0.40 H_2O+0.90 CH_3OH(694.33): C, 51.38; H, 5.78; N, 8.07; Found: C, 51.35; H, 5.83; N, 8.11.

Example 4

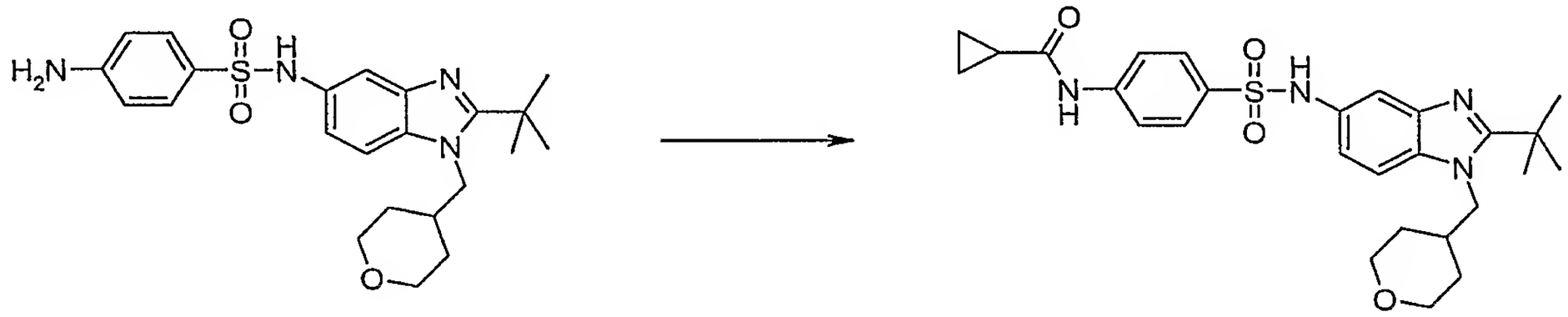
***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2-chloroacetamide**



Following the procedure for Step 1 in Example 1, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (61.8 mg, 0.14 mmol), 2-chloroacetyl chloride (14 uL, 18.9 mg, 0.17 mmol) and DIPEA (39.7 mg, 0.30 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:1-1:4) as eluent. Yield: 57.7 mg (79%); ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.44 - 1.60 (m, 4 H), 1.64 (s, 9 H), 2.23 - 2.40 (m, 1 H), 3.31 - 3.38 (m, 2 H), 3.85 - 3.97 (m, 2 H), 4.16 (s, 2 H), 4.46 (d, J=7.42 Hz, 2 H), 7.26 (dd, J=9.09, 1.66 Hz, 1 H), 7.63 (s, 1 H), 7.66 - 7.72 (m, 2 H), 7.72 - 7.77 (m, 2 H), 7.81 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+ = 519.0$; Anal. Calcd for $C_{25}H_{31}ClN_4O_4S$+1.10 HCl+0.60 EtOAc(612.04): C, 53.77; H, 6.08; N, 9.15; Found: C, 53.81; H, 6.04; N, 9.14.

Example 5

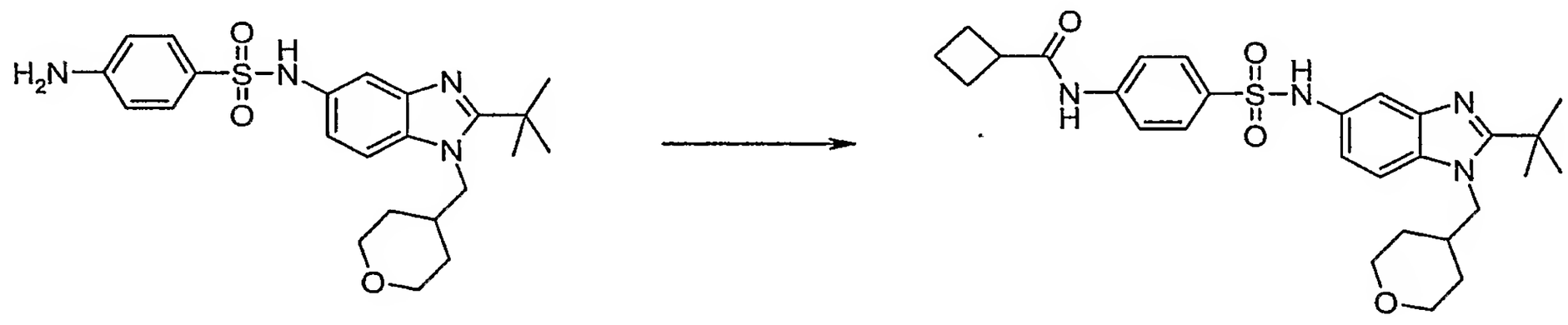
***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]cyclopropanecarboxamide**



Following the procedure for Step 1 in Example 1, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (61.8 mg, 0.14 mmol), cyclopropanecarbonyl chloride (15 uL, 17.5 mg, 0.17 mmol) and DIPEA (39.7 mg, 0.30 mmol) in 10 mL of in DCM. The product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 32.3 mg (37%); ^{1}H NMR (600 MHz, METHANOL-D_4): δ 0.82 - 0.88 (m, 2 H), 0.89 - 0.96 (m, 2 H), 1.45 - 1.60 (m, 4 H), 1.64 (s, 9 H), 1.68 - 1.79 (m, 1 H), 2.22 - 2.40 (m, 1 H), 3.30 - 3.37 (m, 2 H), 3.96 - 3.98 (m, 2 H), 4.45 (d, J=7.42 Hz, 2 H), 7.24 (dd, J=9.09, 1.92 Hz, 1 H), 7.61 (d, J=1.79 Hz, 1 H), 7.64 - 7.68 (m, 2 H), 7.69 - 7.73 (m, 2 H), 7.78 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ = 511.0; Anal. Calcd for $C_{27}H_{34}N_4O_4S$+1.50 TFA+0.60 H_2O (692.54): C, 52.03; H, 5.34; N, 8.09; Found: C, 52.01; H, 5.31; N, 8.14.

Example 6

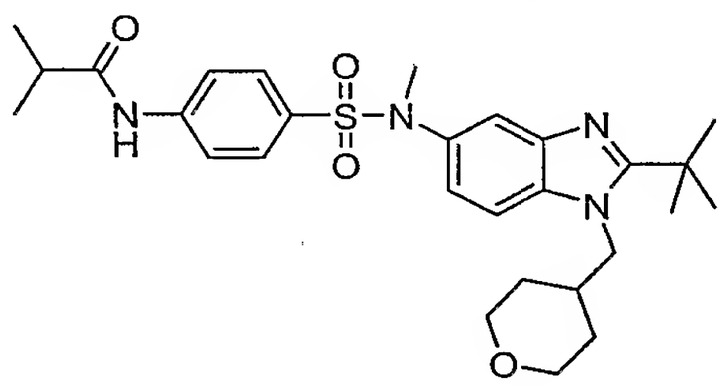
***N*-[4-({[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]cyclobutanecarboxamide**



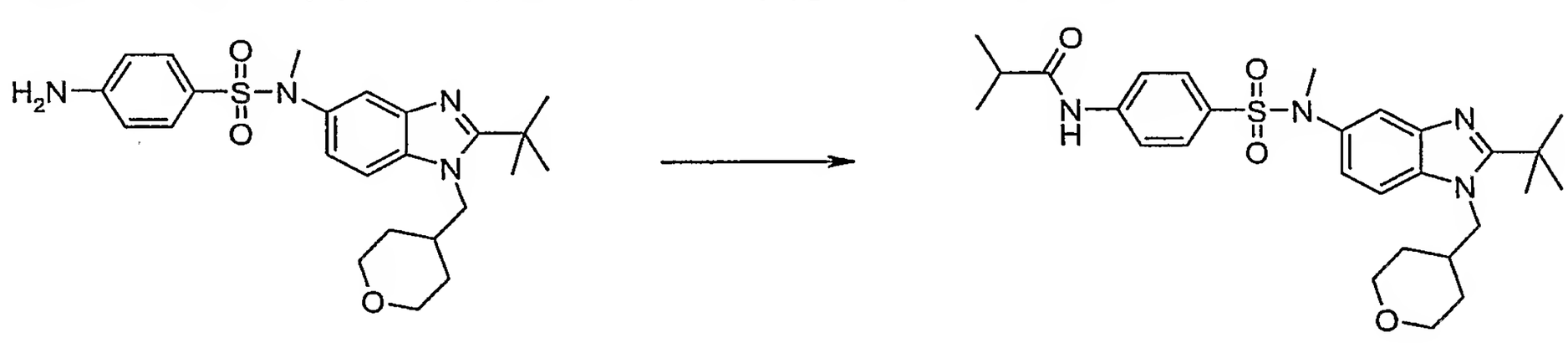
Following the procedure for Step 1 in Example 1, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (61.8 mg, 0.14 mmol), cyclobutanecarbonyl chloride (19 uL, 19.8 mg, 0.17 mmol) and DIPEA (39.7 mg, 0.30 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:1-1:4) as eluent. Yield: 49.6 mg (67% yield); ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.44 - 1.59 (m, 4 H), 1.64 (s, 9 H), 1.82 - 1.91 (m, 1 H), 1.96 - 2.07 (m, 1 H), 2.12 - 2.22 (m, 2 H), 2.22 - 2.38 (m, 3 H), 3.18 - 3.27 (m, 1 H), 3.31 - 3.37 (m, 2 H), 3.90 - 3.92 (m, 2 H), 4.45 (d, J=7.42 Hz, 2 H), 7.24 (dd, J=8.96, 2.05 Hz, 1 H), 7.61 (d, J=2.05 Hz, 1 H), 7.65 - 7.69 (m, 2 H), 7.69 - 7.74 (m, 2 H), 7.79 (d, J=9.22 Hz, 1 H); MS (ESI) $(M+H)^+$ = 525.0; Anal. Calcd for $C_{28}H_{36}N_4O_4S$+1.30 HCl+0.10 H_2O+0.50 EtOAc(617.94): C, 58.31; H, 6.77; N, 9.07; Found: C, 58.28; H, 6.73; N, 9.04.

Example 7

***N*-(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-methylpropanamide**



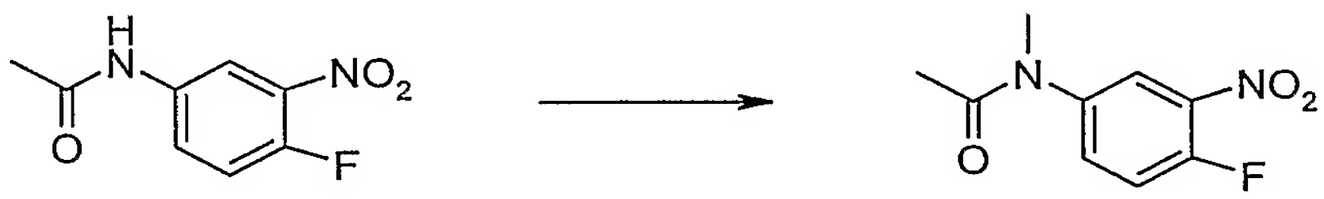
Step A: *N*-(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-methylpropanamide



Isobutyryl chloride (25 uL, 25.2 mg, 0.24 mmol) was added to a solution of DIPEA (75 uL, 55.9 mg, 0.43 mmol) and 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (see following Steps B, C, D, E, F, G and H for preparation) (89.6 mg, 0.20 mmol) in DCM (10 mL) at 0

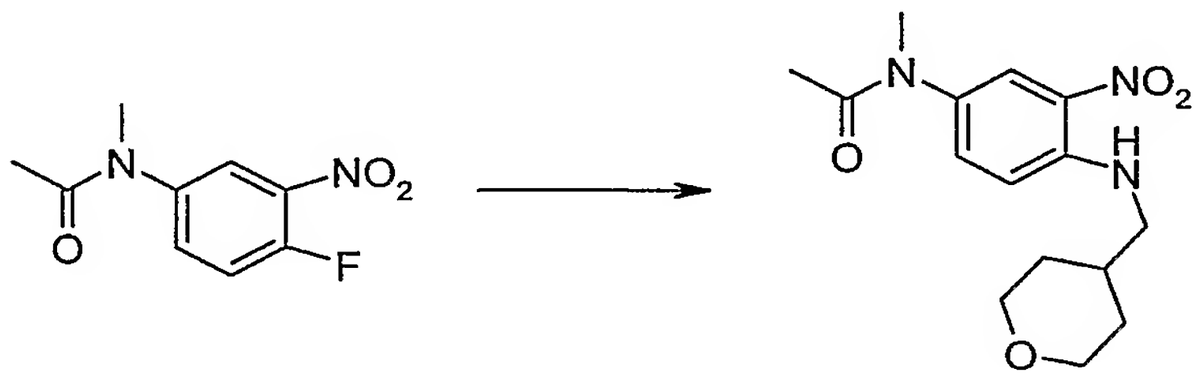
°C. The reaction mixture was stirred for 3 h at rt, quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with DCM (3x5 mL). The combined organic phases were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 86.4 mg (84% yield). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.21 (d, J=6.91 Hz, 6 H), 1.51 - 1.66 (m, 4 H), 1.70 (s, 9 H), 2.26 - 2.46 (m, 1 H), 2.61 - 2.70 (m, 1 H), 3.28 (s, 3 H), 3.34 - 3.43 (m, 2 H), 3.91 - 4.03 (m, 2 H), 4.55 (d, J=7.42 Hz, 2 H), 7.35 (dd, J=8.96, 2.05 Hz, 1 H), 7.43 - 7.51 (m, 2 H), 7.56 (d, J=1.79 Hz, 1 H), 7.71 - 7.77 (m, 2 H), 7.92 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ = 527.0; Anal. Calcd for $C_{28}H_{38}N_4O_4S$+1.50 HCl+0.50 MeOH(597.41): C, 57.30; H, 7.00; N, 9.38; Found: C, 57.32; H, 6.90; N, 9.24.

Step B: *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide



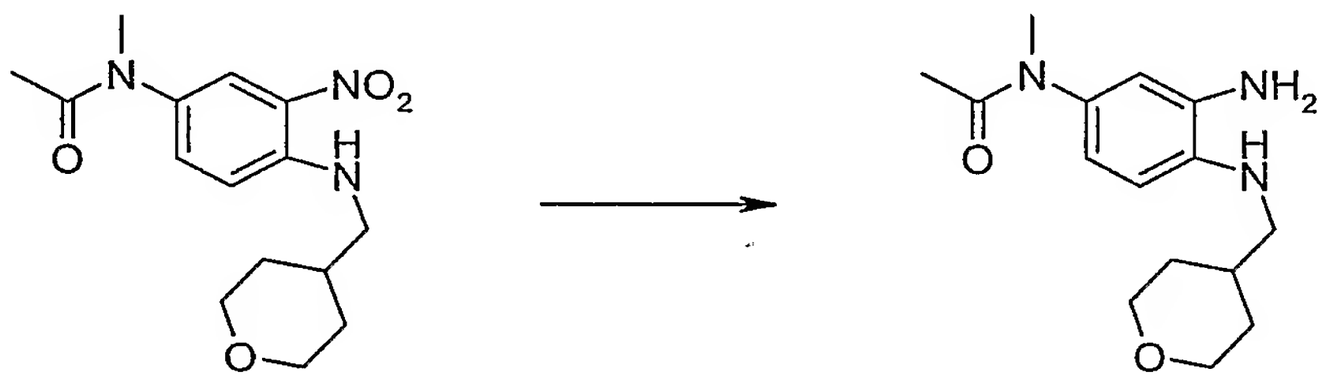
Sodium hydride (4.22 g, 60%, 106 mmol) was added portionwise to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide(13.9 g, 70 mmol) (for preparation, see the step B in Example 1) in THF (200 mL) at 0 °C. Stirring for 20 min, iodomethane (18.5 g, 130 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturaed $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x50 mL). After filtration and concentration, 13.1 g (88%) of the title compound was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

Step C: *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



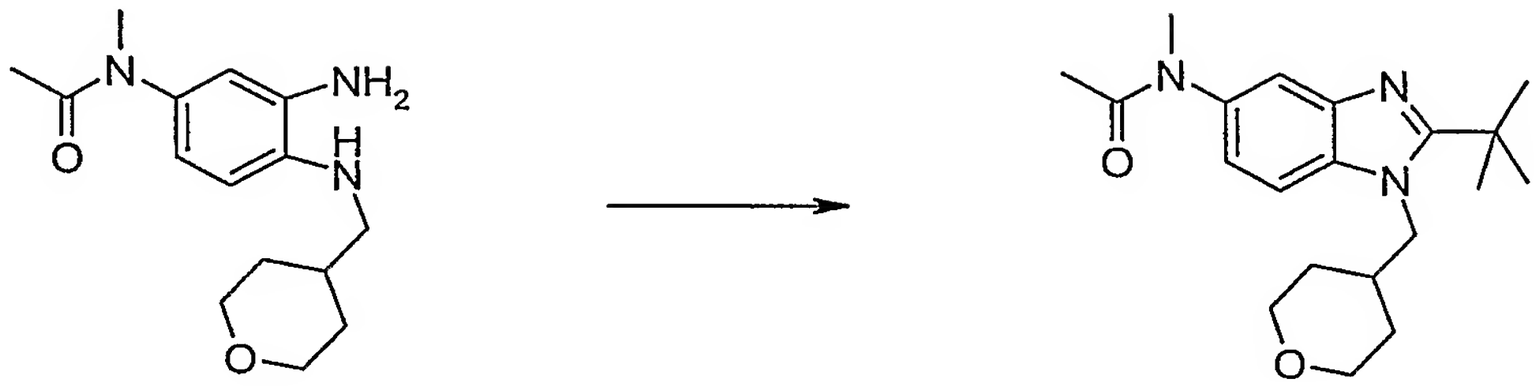
4-Aminomethylpyran (10.0 g, 86.5 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (15.6 g, 73.3 mmol) and TEA (15.3 mL, 11.1 g, 110 mmol) in EtOH (300 mL) at room temperature. The reaction mixture was heated for 6 h at reflux. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H_2O (3x50 mL), saturated NaCl (3x50 mL), and dried over Na_2SO_4. After filtation and concentration, 21.7 g (96%) of the title compound was obtained as an orange-red solid. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H); MS (ESI) $(M+H)^+ = 309.12$.

Step D: *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide



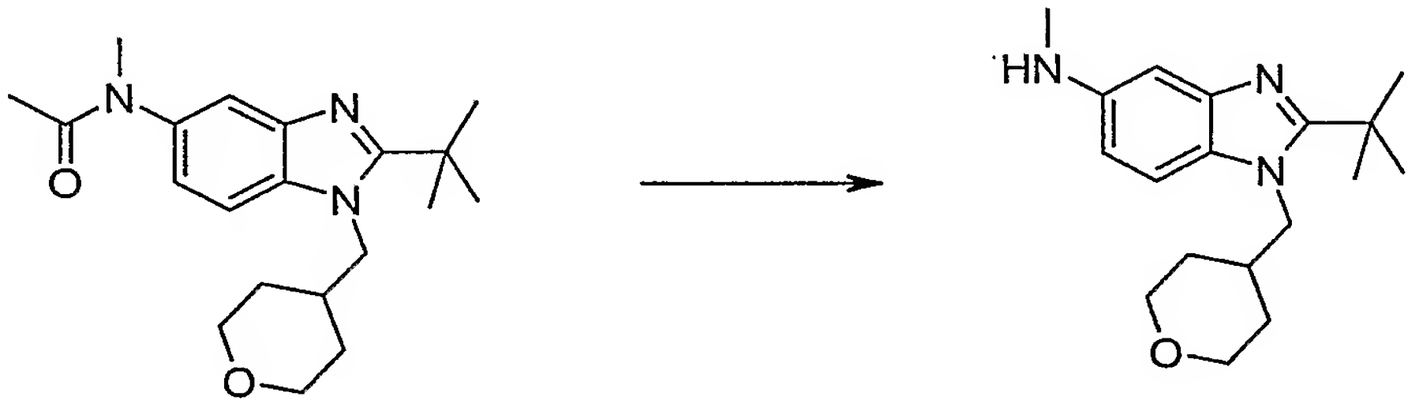
N-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (21.7 g, 70.5 mmol) was hydrogenated in ethyl acetate (500 mL) catalyzed by 10% Pd/C (1.0 g) at 30-40 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 19.6 g (100%) of a purple solid was obtained. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.35 - 1.50 (m, 2 H), 1.67 (s, 1 H), 1.73 - 1.81 (m, 2 H), 1.88 (s, 3 H), 1.88 - 1.99 (m, 1 H), 3.04 (d, *J*=6.64 Hz, 2 H), 3.20 (s, 3 H), 3.33 - 3.48 (m, 4 H), 3.97 - 4.08 (m, 2 H), 6.54 (d, *J*=1.76 Hz, 1 H), 6.60 - 6.63 (m, 2 H); MS (ESI) $(M+H)^+ = 278.7$

Step E: *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



Trimethylacetyl chloride (3.3 mL, 3.20 g, 26.5 mmol) was dropwise added to a solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide (7.01 g, 25.3 mmol)and DIPEA (5.3 mL, 3.92 g, 30.4 mmol) in dichloromethane (170 mL) at 0 °C. The resulting mixture was stirred for 4h at room temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (75 mL) and then divided to 15 sealed test tubes. The mixture was heated at 150°C in a Personal Chemistry SmithSynthesizer microwave instrument for 2.5 h. The combined reaction mixture was evaporated and then dissolved in EtOAc (400 mL), washed with 2 *N* NaOH aqueous solution (2x20 mL), brine (2x20 mL) and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by MPLC using EtOAc/MeOH (10:1) as eluent on silica gel to give 7.31 g (84%) of the title compound as a white solid. MS (ESI) $(M+H)^+ = 344.15$

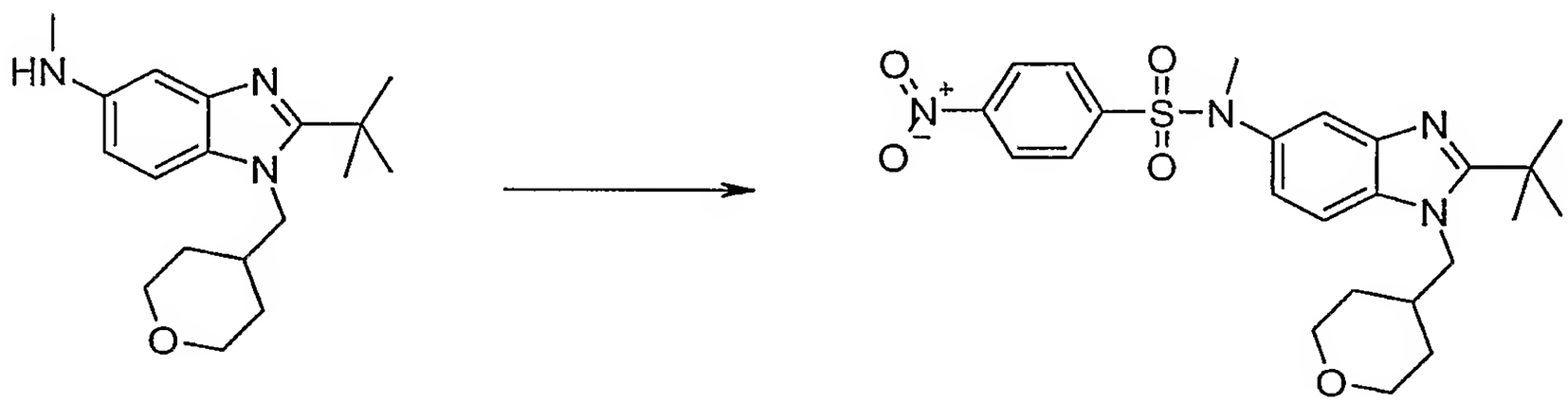
Step F: 2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (4.57g, 13.3 mmol) was dissolved in hydrochloric acid (37%, 100 mL) and then heated overnight at 90-100 °C. Upon concentration, the residue was dissolved in EtOAc and washed with 2*N* NaOH solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 4.01 g (100%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.46 - 1.54 (m, 4 H), 1.54 (s, 9 H), 2.16 - 2.37 (m,

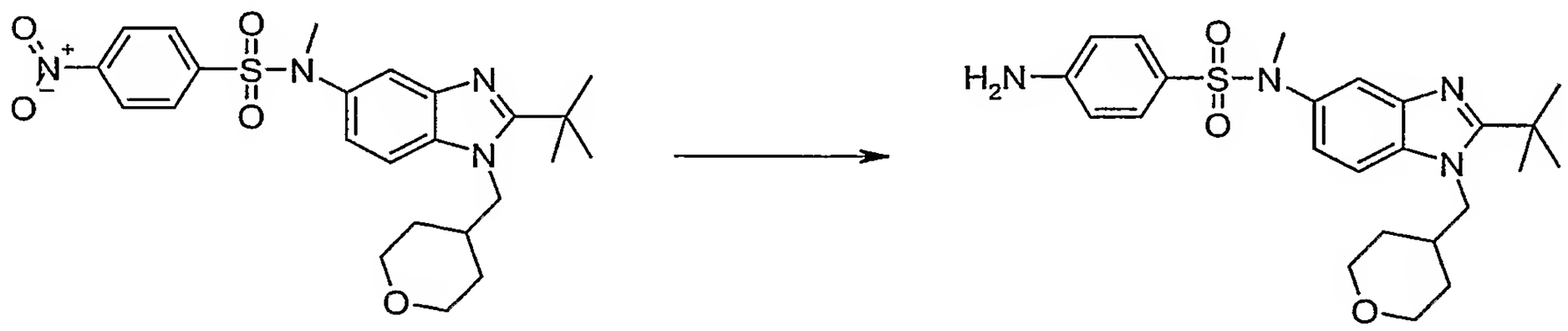
1 H), 2.87 (s, 3 H), 3.23 - 3.38 (m, 2 H), 3.91 - 4.02 (m, 2 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=2.15 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H); MS (ESI) $(M+H)^+$ = 302.06.

Step G: *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



4-Nitrobenzenesulfonyl chloride (1.06 g, 4.8 mmol) was added to a solution of 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-yl-methyl)-1*H*-benzimidazol-5-amine (1.21 g, 4.0 mmol), DIPEA (0.98 mL, 0.72 g, 5.6 mmol) and DMAP (0.10 g, 0.8 mmmol) in 20 mL of DCM. The mixture was stirred overnight at rt, washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using Hex/EtOAc (1:1) as eluent. Yield: 1.91 g (98%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.51 - 1.57 (m, 13 H), 2.24 - 2.34 (m, 1 H), 3.27 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=2.93 Hz, 1 H), 4.02 (t, *J*=3.03 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.19 - 7.23 (m, 2 H), 7.29 - 7.33 (m, 1 H), 7.77 (d, *J*=8.98 Hz, 2 H), 8.30 (d, *J*=8.79 Hz, 2 H).

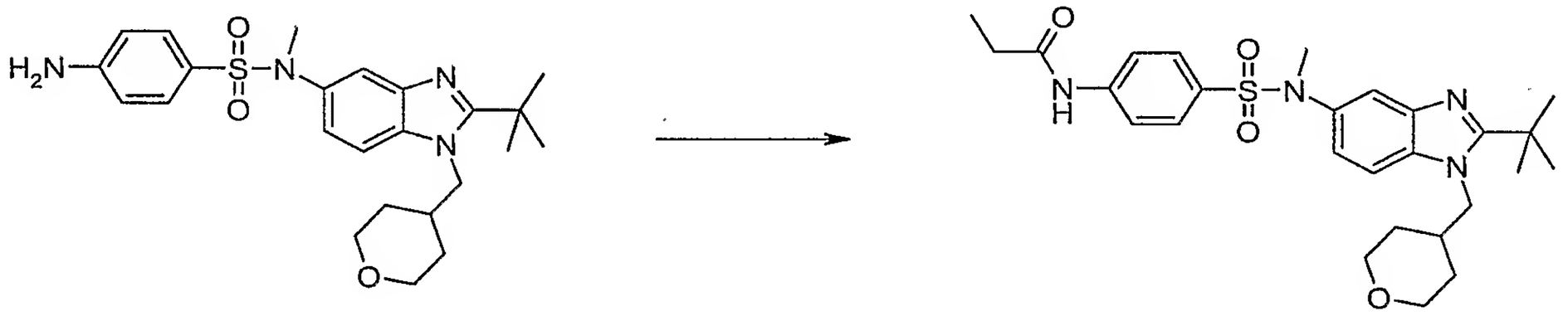
Step H: 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (1.91 g, 3.93 mmol) was dissolved in 200 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 1.80 g (100%). MS (ESI) $(M+H)^+$=457.01.

Example 8

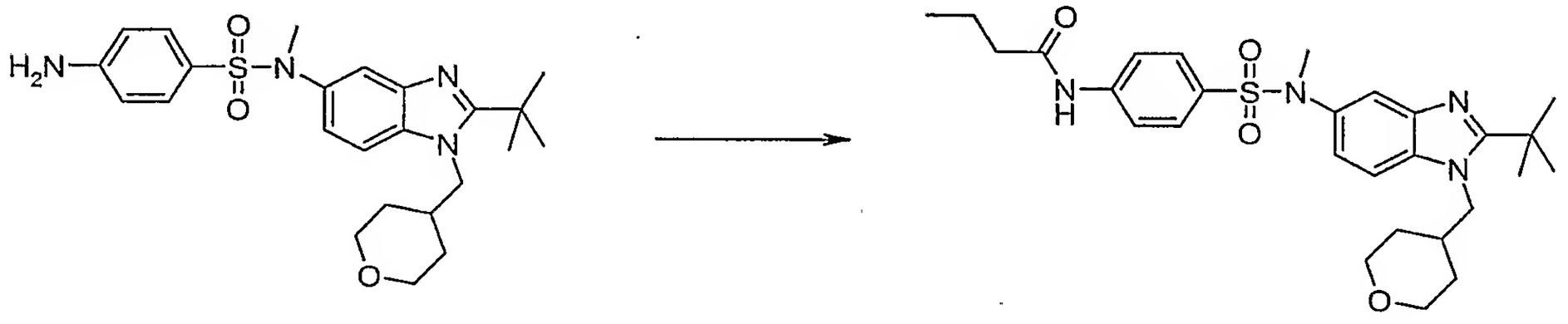
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)propanamide**



Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (89.6 mg, 0.20 mmol), propionyl chloride (21 uL, 21.8 mg, 0.24 mmol) and DIPEA ((75 uL, 55.9 mg, 0.43 mmol) in 10 mL of in DCM. The product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt.. Yield: 68.2 mg (68%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.21 (t, J=7.55 Hz, 3 H), 1.51 - 1.65 (m, 4 H), 1.70 (s, 9 H), 2.33 - 2.42 (m, 1 H), 2.43 (q, J=7.42 Hz, 2 H), 3.27 (s, 3 H), 3.34 - 3.44 (m, 2 H), 3.94 – 3.98 (m, 2 H), 4.54 (d, J=7.68 Hz, 2 H), 7.34 (dd, J=9.09, 1.92 Hz, 1 H), 7.45 - 7.50 (m, 2 H), 7.56 (d, J=1.79 Hz, 1 H), 7.69 - 7.79 (m, 2 H), 7.90 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ = 513.0; Anal. Calcd for $C_{27}H_{36}N_4O_2S$+1.80 TFA+0.20 H_2O +0.20 MeCN(729.73): C, 51.02; H, 5.36; N, 8.06; Found: C, 50.96; H, 5.30; N, 8.02.

Example 9

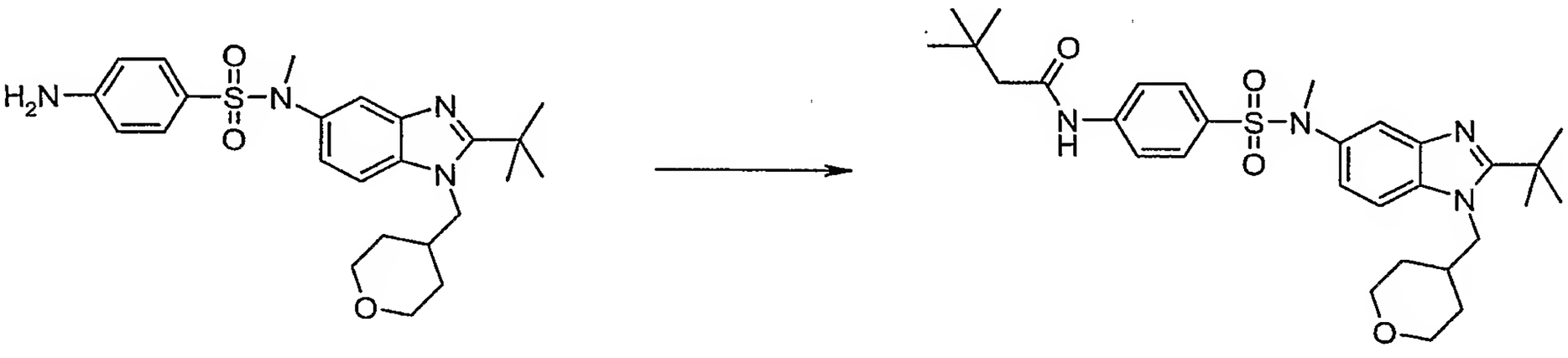
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)butanamide**



Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (89.6 mg, 0.20 mmol), butyryl chloride (25 uL, 25.2 mg, 0.24 mmol) and DIPEA ((75 uL, 55.9 mg, 0.43 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 98.3 mg (95%). ^{1}H NMR (600 MHz, METHANOL-D$_4$): δ 1.01 (t, J=7.42 Hz, 3 H), 1.50 - 1.66 (m, 4 H), 1.70 (s, 9 H), 1.71 - 1.78 (m, 2 H), 2.31 - 2.46 (m, 3 H), 3.28 (s, 3 H), 3.34 - 3.43 (m, 2 H), 3.91 - 4.01 (m, 2 H), 4.55 (d, J=7.42 Hz, 2 H), 7.34 (dd, J=8.96, 2.05 Hz, 1 H), 7.44 - 7.50 (m, 2 H), 7.56 (d, J=1.79 Hz, 1 H), 7.70 - 7.77 (m, 2 H), 7.91 (d, J=9.22 Hz, 1 H); MS (ESI) $(M+H)^+$ = 527.0; Anal. Calcd for $C_{28}H_{38}N_4O_4S$+1.50 HCl+0.50 MeOH(597.41): C, 57.30; H, 7.00; N, 9.38; Found: C, 57.29; H, 6.93; N, 9.23.

Example 10

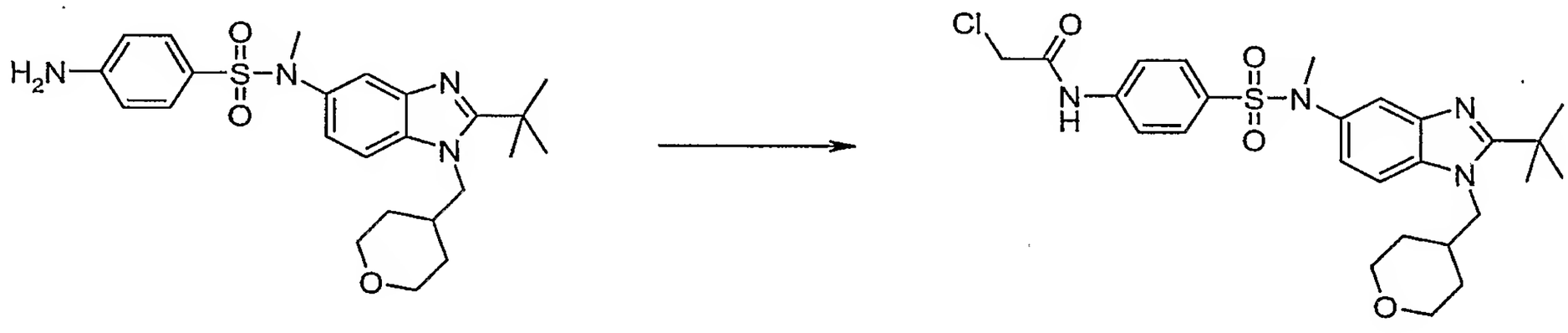
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-3,3-dimethylbutanamide**



Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (89.6 mg, 0.20 mmol), 3,3-dimethylbutyryl chloride (33 uL, 31.8 mg, 0.24 mmol) and DIPEA ((75 uL, 55.9 mg, 0.43 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 107.6 mg (99%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.09 (s, 9 H), 1.50 - 1.67 (m, 4 H), 1.70 (s, 9 H), 2.28 (s, 2 H), 2.32 - 2.49 (m, 1 H), 3.28 (s, 3 H), 3.34 - 3.44 (m, 2 H), 3.92 - 4.06 (m, 2 H), 4.54 (d, J=7.68 Hz, 2 H), 7.35 (dd, J=8.96, 2.05 Hz, 1 H), 7.44 - 7.53 (m, 2 H), 7.56 (d, J=1.79 Hz, 1 H), 7.70 - 7.78 (m, 2 H), 7.90 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+ = 555.0$; Anal. Calcd for $C_{30}H_{42}N_4O_4S$+1.30 HCl+0.40 H_2O +1.00 MeOH(641.40): C, 58.05; H, 7.56; N, 8.74; Found: C, 58.08; H, 7.55; N, 8.73.

Example 11

***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-chloroacetamide**

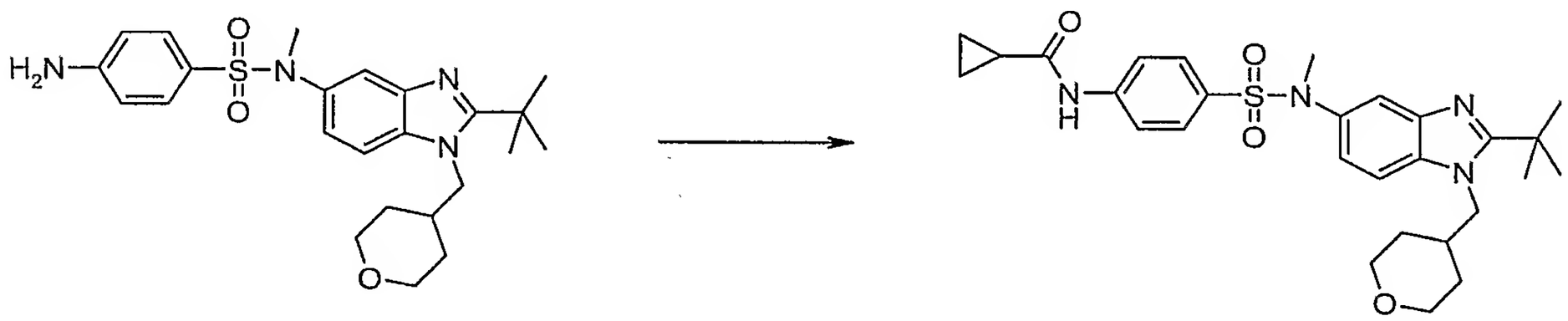


Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (69.8 mg, 0.15 mmol), 2-chloroacetyl chloride (14 uL, 20.3 mg, 0.18 mmol) and DIPEA (57 uL, 42.3 mg, 0.33 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 80.0 mg (100%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.51 - 1.66 (m, 4 H), 1.70 (s, 9 H), 2.31 - 2.49 (m, 1 H), 3.29 (s, 3 H), 3.34 - 3.43 (m, 2 H), 3.90 - 4.03 (m, 2 H), 4.22 (s, 2 H), 4.55 (d, J=7.42 Hz, 2 H), 7.35 (dd, J=9.09, 1.92 Hz, 1 H), 7.46 - 7.54 (m, 2 H), 7.57 (d, J=2.05 Hz, 1 H), 7.73 - 7.80 (m, 2 H), 7.92 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+ = 533.0$; Anal. Calcd for $C_{26}H_{33}ClN_4O_4S$+0.90

HCl+0.80 MeOH (591.54): C, 54.42; H, 6.32; N, 9.47; Found: C, 54.53; H, 6.13; N, 9.22..

Example 12

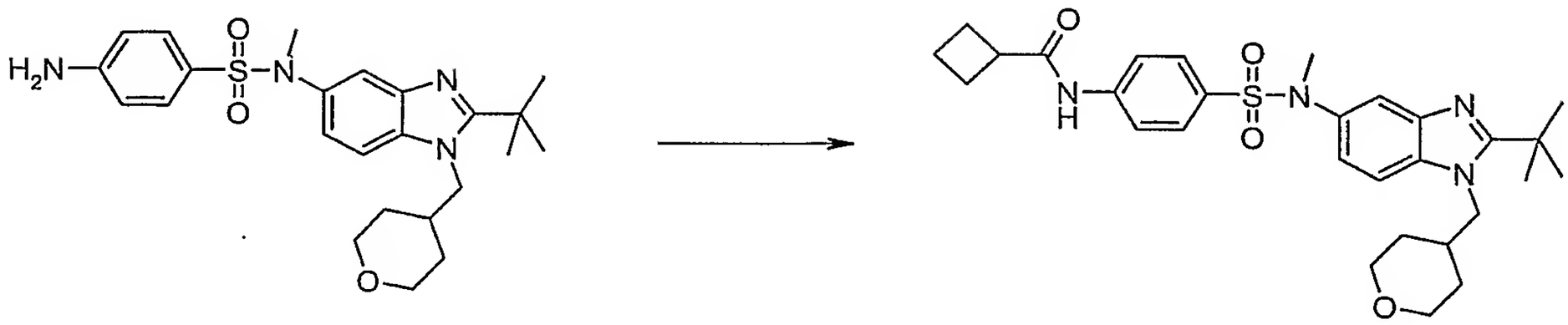
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)cyclopropanecarboxamide**



Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (69.8 mg, 0.15 mmol), cyclopropanecarbonyl chloride (16 uL, 18.8 mg, 0.18 mmol) and DIPEA (57 uL, 42.3 mg, 0.33 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 75.2 mg (96%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 0.87 - 0.93 (m, 2 H), 0.95 - 1.03 (m, 2 H), 1.52 - 1.65 (m, 4 H), 1.70 (s, 9 H), 1.76 - 1.86 (m, 1 H), 2.28 - 2.48 (m, 1 H), 3.28 (s, 3 H), 3.34 - 3.43 (m, 2 H), 3.95 - 3.97 (m, 2 H), 4.54 (d, J=7.42 Hz, 2 H), 7.34 (dd, J=8.96, 2.05 Hz, 1 H), 7.42 - 7.50 (m, 2 H), 7.55 (d, J=1.54 Hz, 1 H), 7.68 - 7.79 (m, 2 H), 7.90 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+ = 525.0$; Anal. Calcd for $C_{28}H_{36}N_4O_4S$+1.30 HCl+0.80 MeOH (597.72): C, 57.87; H, 6.83; N, 9.37; Found: C, 57.90; H, 6.69; N, 9.30.

Example 13

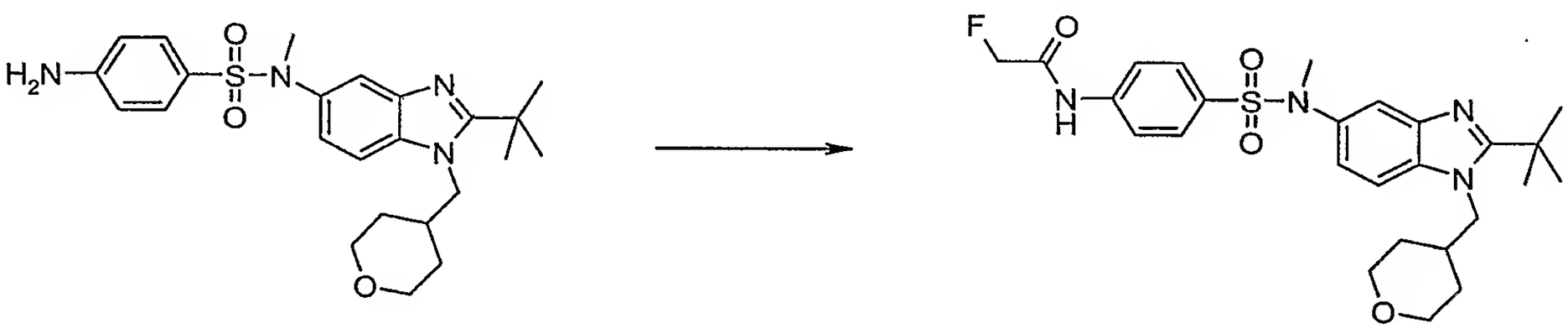
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)cyclobutanecarboxamide**



Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (69.8 mg, 0.15 mmol), cyclobutanecarbonyl chloride (21 uL, 21.3 mg, 0.18 mmol) and DIPEA (57 uL, 42.3 mg, 0.33 mmol) in 10 mL of in DCM. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 80.1 mg (99%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.52 - 1.64 (m, 4 H), 1.69 (s, 9 H), 1.87 - 1.97 (m, 1 H), 2.01 - 2.10 (m, 1 H), 2.18 - 2.27 (m, 3 H), 2.29 - 2.37 (m, 2 H), 2.37 - 2.45 (m, 1 H), 3.27 (s, 3 H) 3.34 - 3.43 (m, 2 H), 3.96 - 3.98 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.32 (dd, J=8.96, 2.05 Hz, 1 H), 7.44 - 7.50 (m, 2 H), 7.54 (d, J=1.79 Hz, 1 H), 7.71 - 7.80 (m, 2 H), 7.88 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ = 539.0; Anal. Calcd for $C_{29}H_{38}N_4O_4S$+1.0 HCl+0.70 MeOH (597.60): C, 59.69; H, 7.05; N, 9.38; Found: C, 59.75; H, 6.90; N, 9.29.

Example 14

***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-fluoroacetamide**

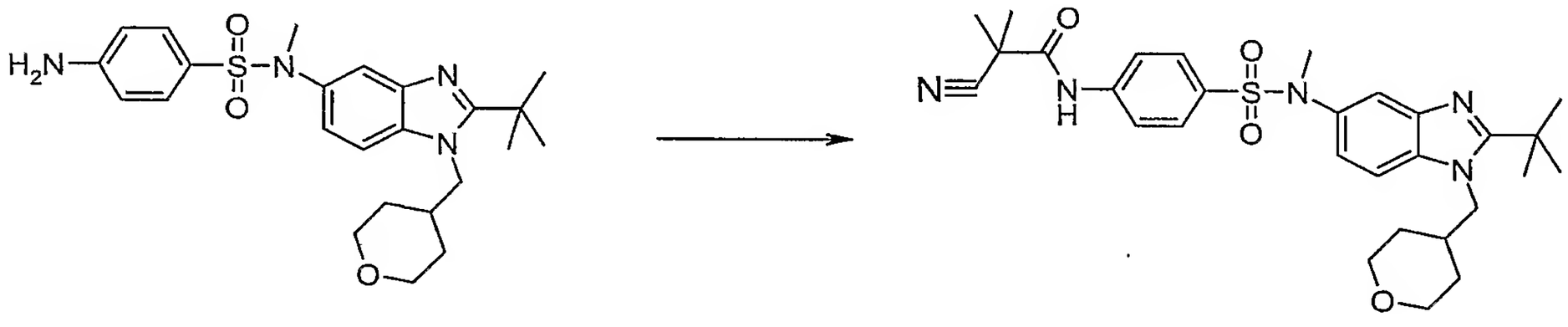


Following the procedure for Step A in Example 7, using 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (35.7 mg, 0.075 mmol), 2-fluoroacetyl chloride (8.7 mg, 0.09 mmol) and DIPEA (29 uL, 21.3 mg, 0.17 mmol) in 10 mL of in DCM. The

product was purified by silica gel flash chromatography using Hex/EtOAc (1:2) as eluent. Yield: 17.0 mg (44%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.47 - 1.60 (m, 4 H), 1.64 (s, 9 H), 2.26 - 2.43 (m, 1 H), 3.24 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.91 - 3.94 (m, 2 H), 4.48 (d, J=7.42 Hz, 2 H), 4.94 (d, J=46.87 Hz, 2 H), 7.27 (dd, J=8.89, 1.86 Hz, 1 H), 7.44 - 7.49 (m, 2 H), 7.50 (d, J=1.76 Hz, 1 H), 7.76 - 7.80 (m, 2 H), 7.83 (d, J=8.79 Hz, 1 H); MS (ESI) $(M+H)^+$ = 517.0; Anal. Calcd for $C_{26}H_{33}FN_4O_4S$+0.80 TFA+ 0.30 H_2O+0.70 EtOAc(674.94): C, 54.10; H, 5.97; N, 8.30; Found: C, 54.09; H, 6.01; N, 8.28.

Example 15

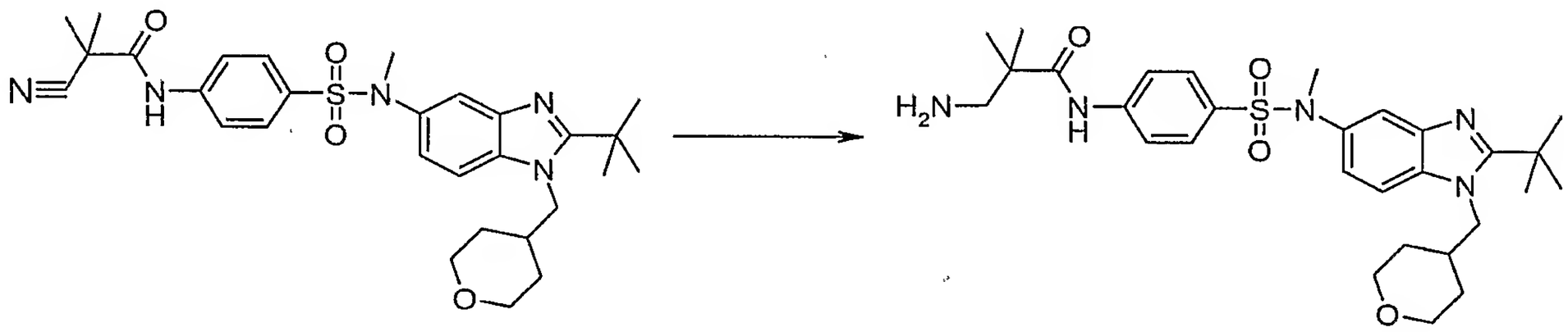
***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-cyano-2-methylpropanamide**



DIPEA (114 uL, 85.3 mg, 0.66 mmol) was added to a solution of 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (137.0 mg, 0.30 mmol) and 2-cyano-2-methylpropanoic acid (37.3 mg, 0.33 mmol) in 10 mL of DMF. Stirrring for 20 min, HATU (136.9 mg, 0.36 mmol) was added at 0 °C. The reaction mixture was stirred for two days at rt, quenched with H_2O (100 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine solution and dried over Na_2SO_4. The product was purified by silica gel flash chromatography using Hex/EtOAc (1:1) as eluent. Yield: 165.2 mg (99%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.52 - 1.65 (m, 4 H), 1.70 (s, 15 H), 2.29 - 2.47 (m, 1 H), 3.29 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.91 - 4.05 (m, 2 H), 4.54 (d, J=7.42 Hz, 2 H), 7.33 (d, J=8.96 Hz, 1 H), 7.48 - 7.54 (m, 2 H), 7.54 (s, 1 H), 7.78 - 7.84 (m, 2 H), 7.89 (d, J=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ = 552.0; Anal. Calcd for $C_{29}H_{37}N_5O_5S$+5.10 HCl(737.66): C, 47.22; H, 5.75; N, 9.49; Found: C, 47.19; H, 5.49; N, 9.43.

Example 16

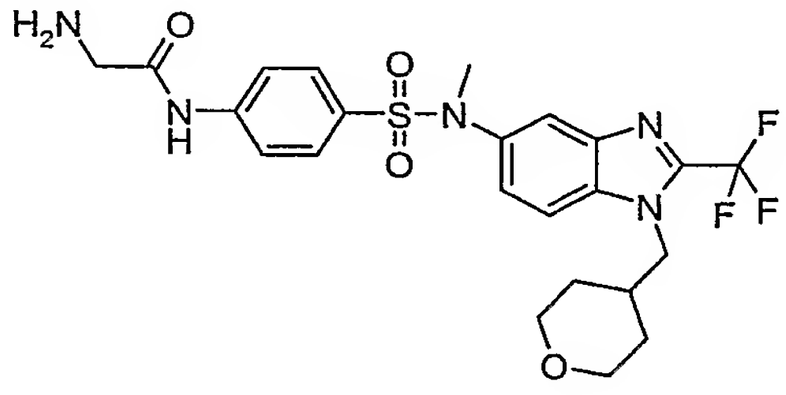
3-Amino-*N*-(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2,2-dimethylpropanamide



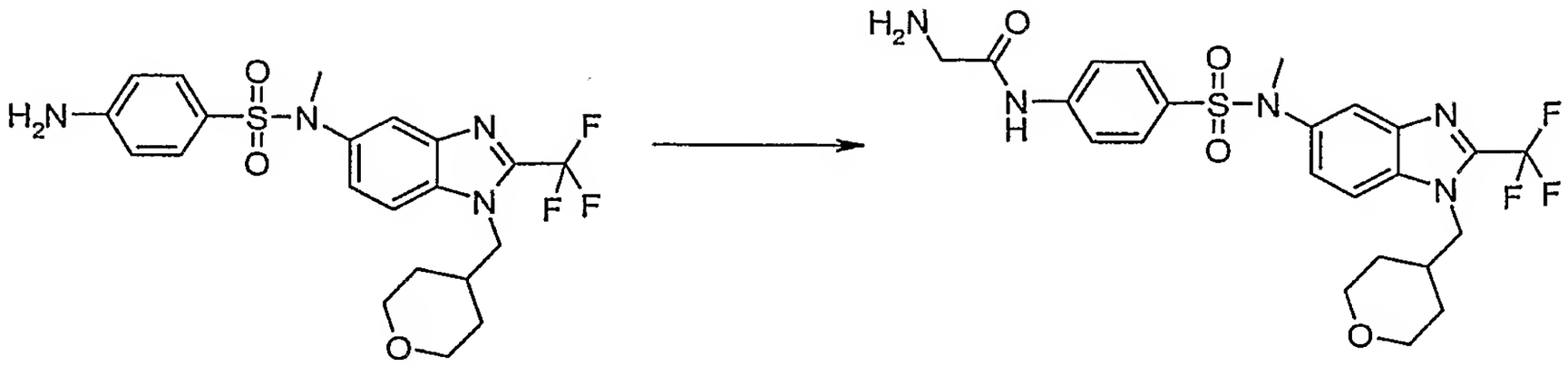
N-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-cyano-2-methylpropanamide (124 mg, 0.22 mmol) was dissolved in 20 mL of EtOH containing a catalytic amount of Raney-Ni. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 122 mg (100%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.44 (s, 6 H), 1.47 - 1.62 (m, 4 H), 1.66 (s, 9 H), 2.24 - 2.47 (m, 1 H), 3.11 (s, 2 H), 3.26 (s, 3 H), 3.32 - 3.41 (m, 2 H), 3.91 - 4.00 (m, 2 H), 4.49 (d, J=7.62 Hz, 2 H), 7.25 (dd, J=8.98, 1.95 Hz, 1 H), 7.46 - 7.52 (m, 2 H), 7.54 (d, J=1.95 Hz, 1 H), 7.77 - 7.85 (m, 3 H); MS (ESI) $(M+H)^+$ = 556.0; Anal. Calcd for $C_{29}H_{41}N_5O_4S$+2.90 TFA+0.70 H_2O(899.02): C, 46.49; H, 5.08; N, 7.79; Found: C, 46.44; H, 5.03; N, 7.87.

Example 17

N^1-[4-({Methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]glycinamide

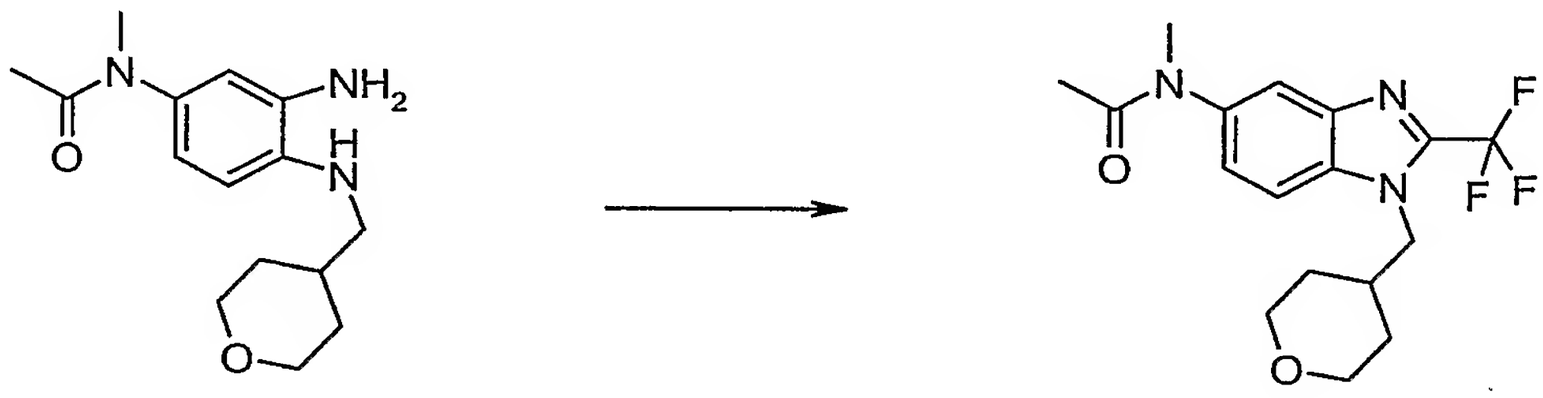


Step A: N^1-[4-({Methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]glycinamide



A solution of 4-amino-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (42.0 mg, 0.09 mmol) (see following Steps B, C, D, and E for preparation), *N*-(*tert*-butoxycarbonyl)glycine (31.4 mg, 0.18 mmol), DIPEA (35 uL, 25.5 mg, 0.20 mmol) and HATU (76.0 mg, 0.18 mmol) in DMF (3 mL) was stirred for two days at room temperature, diluted with EtOAc (50 mL), washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4. Upon concentration, the residue was dissolved in DCM (3 mL) and treated with TFA (3 mL). After evaporation of solvent, the product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt.. Yield: 22.9 mg (40%). ^{1}H NMR (600 MHz, METHANOL-D_4): δ 1.37 - 1.56 (m, 4 H), 2.14 - 2.37 (m, 1 H), 3.25 (s, 3 H), 3.31 - 3.42 (m, 2 H), 3.88 (s, 2 H), 3.90 - 3.99 (m, 2 H), 4.32 (d, J=7.81 Hz, 2 H), 7.33 (d, J=1.76 Hz, 1 H), 7.39 (dd, J=8.88, 2.05 Hz, 1 H), 7.47 - 7.55 (m, 2 H), 7.67 - 7.81 (m, 3 H); MS (ESI) $(M+H)^+$ = 526.0. nal. Calcd for $C_{23}H_{26}F_3N_5O_4S$+ 1.50 TFA+0.40 H_2O +0.20 CH3CN (712.01): C, 44.54; H, 4.09; N, 10.23; Found: C, 44.50 ; H, 4.12; N, 10.24.

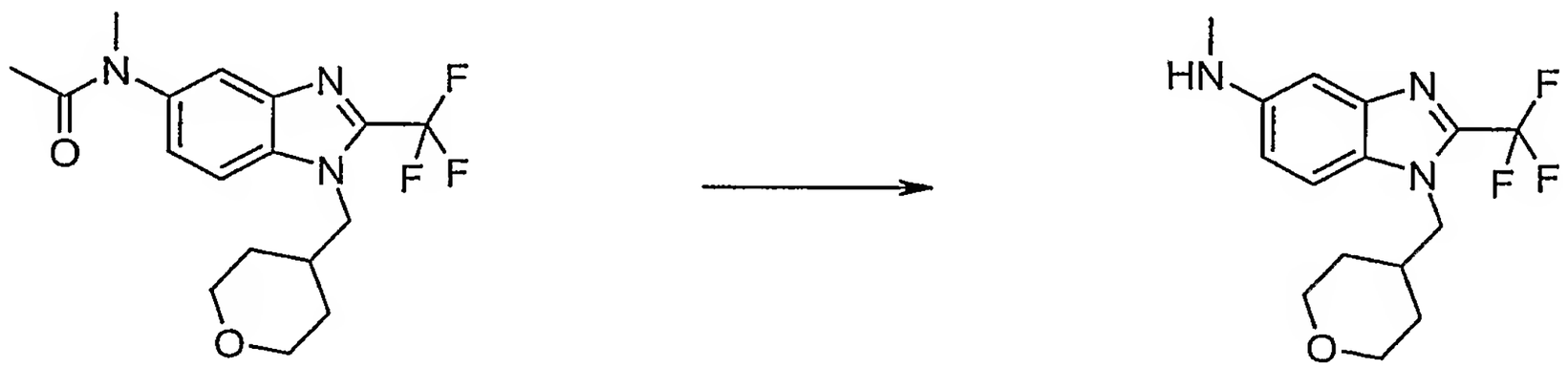
Step B: *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide



A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide (2.77 g, 10 mmol) in trifluoroacetic acid (60 mL) was heated for 18 h at reflux. After evaporation of the solvent, the residue was dissolved in EtOAc, and washed with 2*N* NaOH, and dried over Na_2SO_4. The desired product was purified by

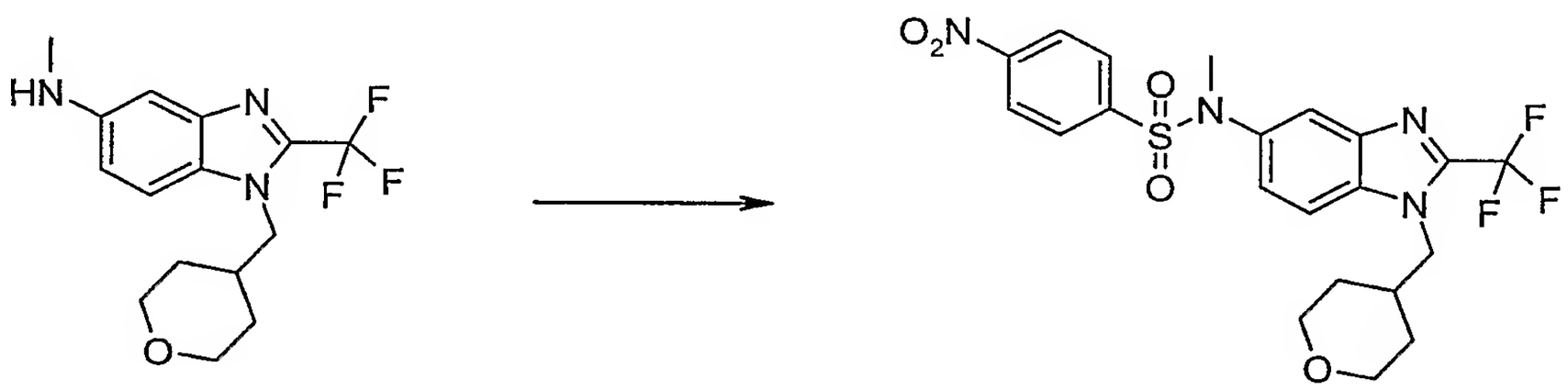
silica gel flash chromatography using EtOAc as eluent. Yield: 3.18g (90%). MS (ESI) $(M+H)^+ = 355.98$.

Step C: *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine



A solution of *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide (1.78 g, 4.54 mmol) in hydrochloric acid (37%, 40 mL) was heated overnight at 90 °C. After concentration and dried *in vacuo*, 1.59 g of a crude product was obtained as HCl salt, which was used directly at Step D. MS (ESI) $(M+H)^+ = 314.20$.

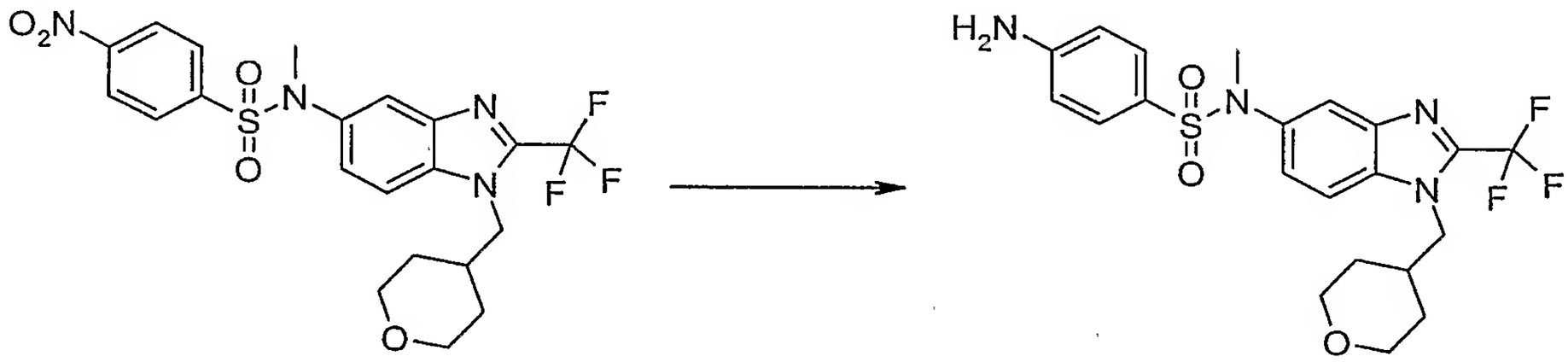
Step D: *N*-methyl-4-nitro-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



4-Nitrobenzenesulfonyl chloride (1.24 g, 5.04 mmol) was added to a solution of *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine hydrochloride (1.48 g, 4.23 mmol), DMAP (0.19 g, 1.57 mmol) and DIPEA (2.9 mL, 2.19 g, 16.9 mmol) in MeCN (60 mL) at 0 °C. The mixture was stirred overnight at room temperature, diluted with EtOAc (400 mL), washed with H_2O (2x20 mL), $NaHCO_3$ (2x20 mL), brine (2x20 mL) and dried over Na_2SO_4. The crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 1.43 g (68%) of a yellow solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.39 - 1.54 (m, 4 H), 2.14 - 2.34 (m, 1 H), 3.32 (s, 3 H), 3.33 - 3.40 (m, 2 H),

3.86 - 4.01 (m, 2 H), 4.32 (d, J=7.42 Hz, 2 H), 7.31 (dd, J=8.88, 2.05 Hz, 1 H), 7.45 (d, J=2.15 Hz, 1 H), 7.74 (d, J=8.98 Hz, 1 H), 7.76 - 7.82 (m, 2 H), 8.27 - 8.42 (m, 2 H). MS (ESI) $(M+H)^+$ = 499.0. Anal. Calcd for $C_{21}H_{21}F_3N_4O_5S$+ 0.50 TFA+0.20 H_2O (559.10): C, 47.26; H, 3.95; N, 10.02; Found: C, 47.24; H, 3.80; N, 10.20.

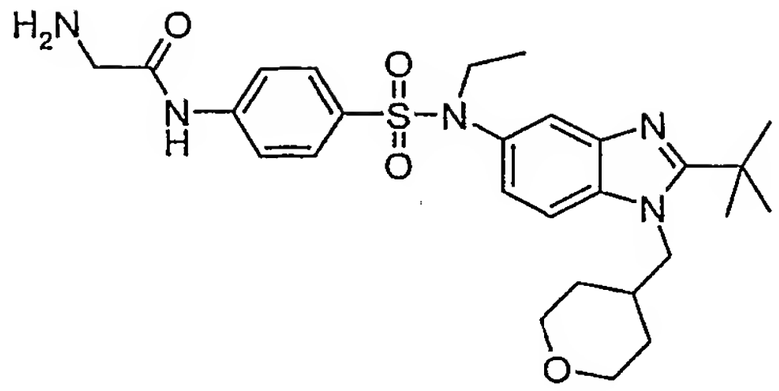
Step E: 4-Amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



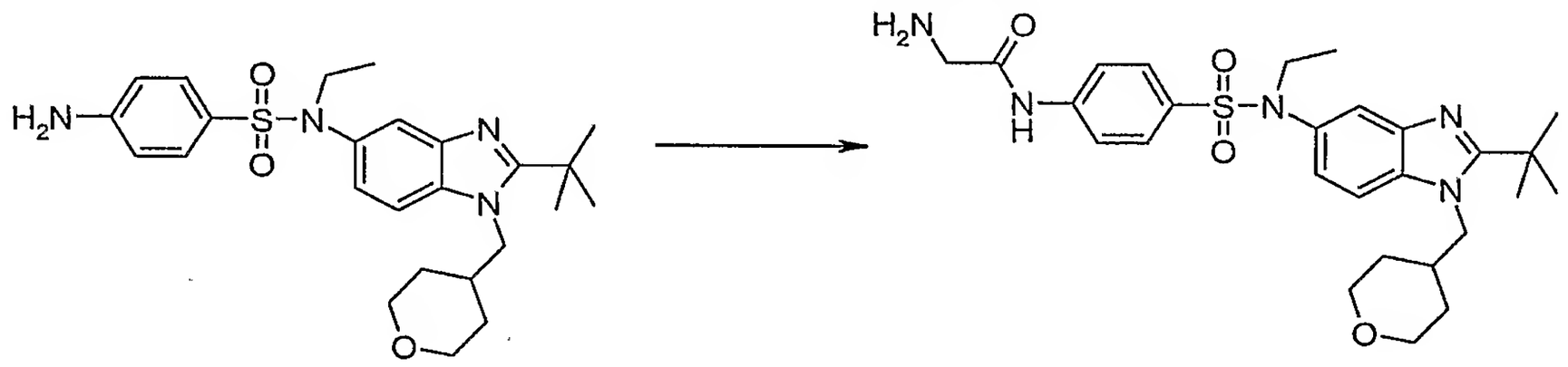
N-Methyl-4-nitro-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (1.43 g, 2.87 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.5 mg) at 30-40 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 1.32 g (98%) of a white solid was obtained. A small amount of the crude product was purified by reversed-phase HPLC using 20-70% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.38 - 1.55 (m, 4 H), 2.15 - 2.35 (m, 1 H), 3.18 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.82 - 4.02 (m, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 6.58 - 6.69 (m, 2 H), 7.15 - 7.23 (m, 2 H), 7.35 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 (d, J=1.56 Hz, 1 H), 7.71 (d, J=8.79 Hz, 1 H). MS (ESI) $(M+H)^+$ = 469.0. Anal. Calcd for $C_{21}H_{23}F_3N_4O_3S$+ 0.40 TFA (514.11): C, 50.93; H, 4.59; N, 10.90; Found: C, 51.00; H, 4.72; N, 10.54.

Example 18

N^1-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl}phenyl)glycinamide



Step A: N^1-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](ethyl)amino]sulfonyl}phenyl)glycinamide

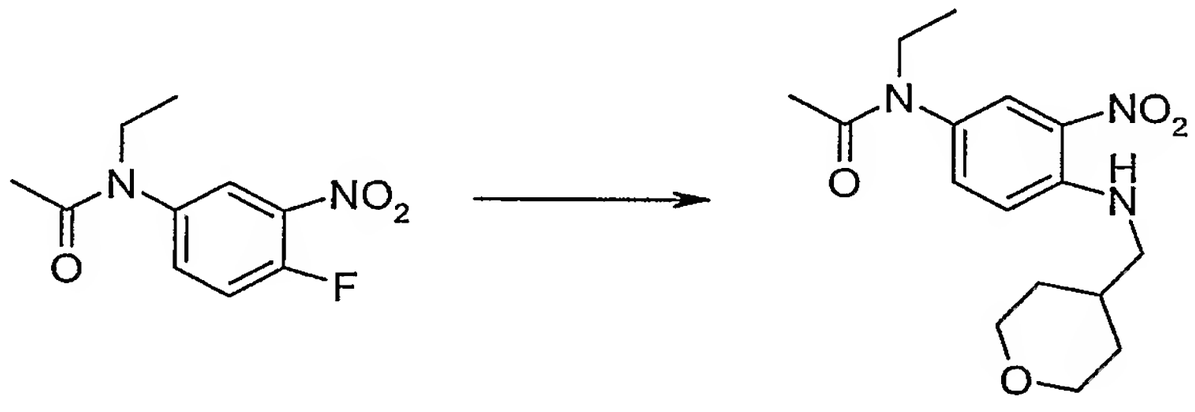


A solution of 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide (85.1 mg, 0.15 mmol) (see following Steps B, C, D, E, F and G for preparation), *N*-(*tert*-butoxycarbonyl)glycine (52.6 mg, 0.30 mmol), DIPEA (57 uL, 42.7 mg, 0.33 mmol) and HATU (125.5 mg, 0.30 mmol) in DMF (5 mL) was stirred over weekend at room temperature, diluted with EtOAc (50 mL), washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4. Upon concentration, the crude product was purified by MPLC using EtOAc on silica gel to give 103.3 mg of a white solid, which was treated with 5 mL of 4*N* HCl in dioxane. After evaporation of solvent, the product was purified by reversed-phase HPLC using 10-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 87.3 mg (91%). ^{1}H NMR (400 MHz, METHANOL-D_4): δ 1.07 (t, J=7.03 Hz, 3 H), 1.51 - 1.62 (m, 4 H), 1.68 (s, 9 H), 2.26 - 2.49 (m, 1 H), 3.32 - 3.41 (m, 2 H), 3.72 (q, J=7.29 Hz, 2 H), 3.90 (s, 2 H), 3.92 - 3.99 (m, 2 H), 4.52 (d, J=7.62 Hz, 2 H), 7.22 (dd, J=8.98, 1.95 Hz, 1 H), 7.53 - 7.61 (m, 3 H), 7.73 - 7.81 (m, 2 H), 7.88 (d, J=8.79 Hz, 1 H); MS (ESI) $(M+H)^+ = 528.0$; Anal. Calcd for $C_{27}H_{37}N_5O_4S$+ 2.60 TFA+4.00 H_2O +0.80 CH_3CN (929.06): C, 43.70; H, 5.42; N, 8.74; Found: C, 43.66 ; H, 5.46; N, 8.78.

Step B: *N*-Ethyl-*N*-(4-fluoro-3-nitrophenyl)acetamide

Sodium hydride (1.20g, 30 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide(3.96 g, 20 mmol) (for preparation see the step B in Example 1) in THF (100 mL) at 0 °C. Stirring for 20 min, iodoethane (9.32 g, 60 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with saturated $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, the residue was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 2.36 g (52%) of a yellow solid as the title compound. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.14 (t, J=6.93 Hz, 3 H), 1.88 (s, 3 H), 3.77 (q, J=7.0 Hz, 2 H), 7.34 – 7.43 (m, 1 H), 7.48 (s, 1 H), 7.87 – 7.98 (m, 1 H).

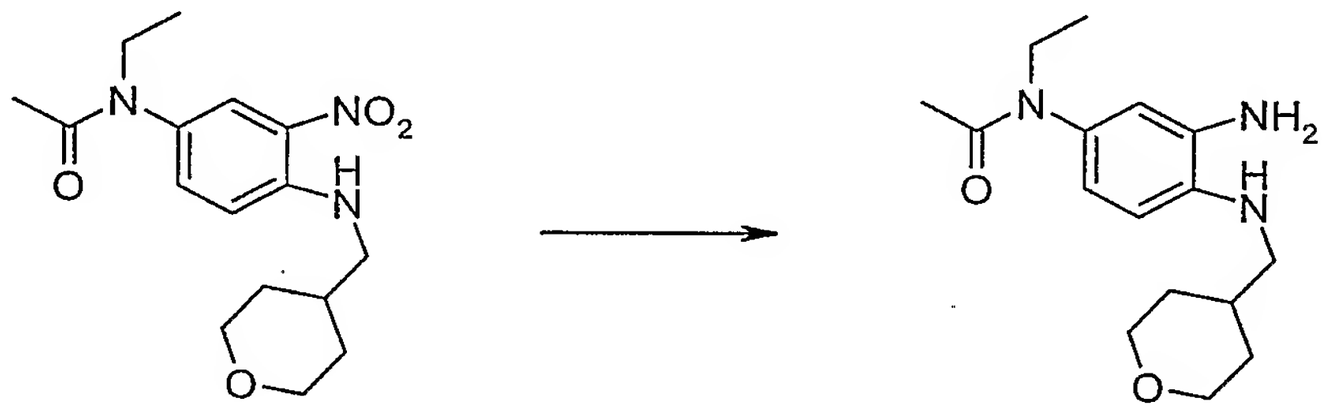
Step C: *N*-Ethyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



4-Aminomethyltetrahydropyran (1.32 g, 11.4 mmol) was added to a mixture of *N*-ethyl-*N*-(4-fluoro-3-nitrophenyl)acetamide (2.36 g, 10.4 mmol) and sodium carbonate (2.43 g, 22.9 mmol) in EtOH (70 mL) at room temperature. The reaction mixture was heated for a wewo days at 60 °C. Upon evaporation of ethanol, the residue was diluted with H_2O (50 mL), and extracted with EtOAc (3x100 mL). The combined organic phases weer washed saturated NaCl (2x50 mL) and dried over Na_2SO_4. After filtation and concentration, the residue was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 2.83 g (85%) of an orange-red solid as the title compound. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.11 (t, *J*=7.13 Hz, 3 H), 1.38 - 1.52 (m, 2 H), 1.78 (m, 2 H), 1.86 (s, 3 H), 1.92 - 2.04 (m, 1 H), 3.20 - 3.29 (m, 2 H), 3.39 - 3.49 (m,

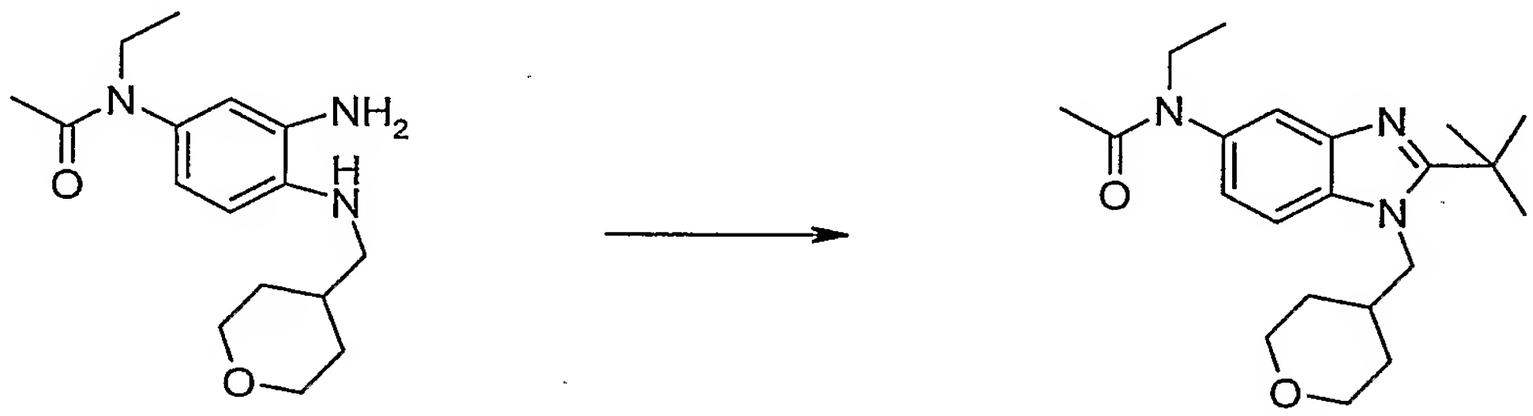
2 H), 3.71 (q, *J*=7.09 Hz, 2 H), 4.00 - 4.08 (m, 2 H), 6.91 (d, *J*=8.98 Hz, 1 H), 7.24 (d, *J*=2.54 Hz, 1 H), 8.01 (d, *J*=2.54 Hz, 1 H), 8.22 (t, *J*=4.98 Hz, 1 H).

Step D: *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide



N-Ethyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (2.83 g, 8.79 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi H_2 in Parr shaker for 16 h at room temperature. After filtration through celite and concentration, 2.45 g (95%) of a light yellow solid was obtained, which was used in the next step without purification. MS (ESI) $(M+H)^+$ = 292.3

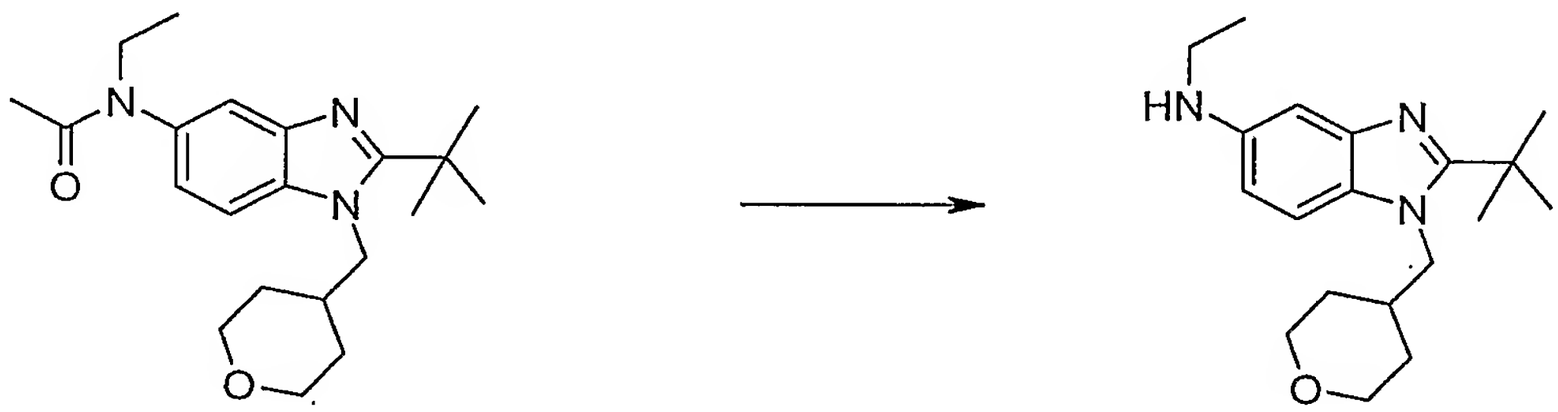
Step E: *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylacetamide



Following the procedure for Step E in Example 7, using *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-ethylacetamide (803.1 mg, 2.75 mmol), DMAP (671.9 mg, 5.50 mmol) and trimethylacetyl chloride (380.9 mg, 3.16 mmol) in DCM (60 mL) and then in DCE (30 mL), the crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel. Yield: 694.1 mg (71%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.12 (t, *J*=7.13 Hz, 3 H), 1.51 - 1.57 (m, 4 H), 1.58 (s, 9 H), 1.83 (s, 3 H), 2.21 - 2.40 (m, 1 H), 3.26 - 3.43 (m, 2 H), 3.78 (q, *J*=7.23 Hz, 2

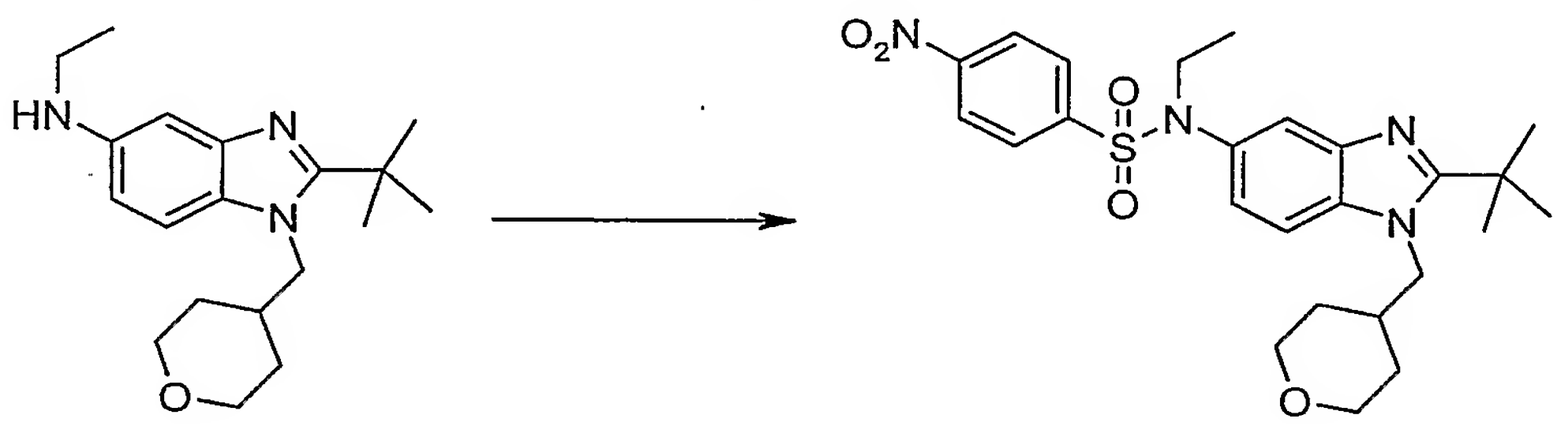
H), 3.94 - 4.07 (m, 2 H), 4.22 (d, *J*=7.42 Hz, 2 H), 7.02 (dd, *J*=8.59, 1.95 Hz, 1 H), 7.34 (d, *J*=8.59 Hz, 1 H), 7.54 (d, *J*=0.98 Hz, 1 H). MS (ESI) $(M+H)^+ = 358.07$.

Step F: 2-*tert*-Butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



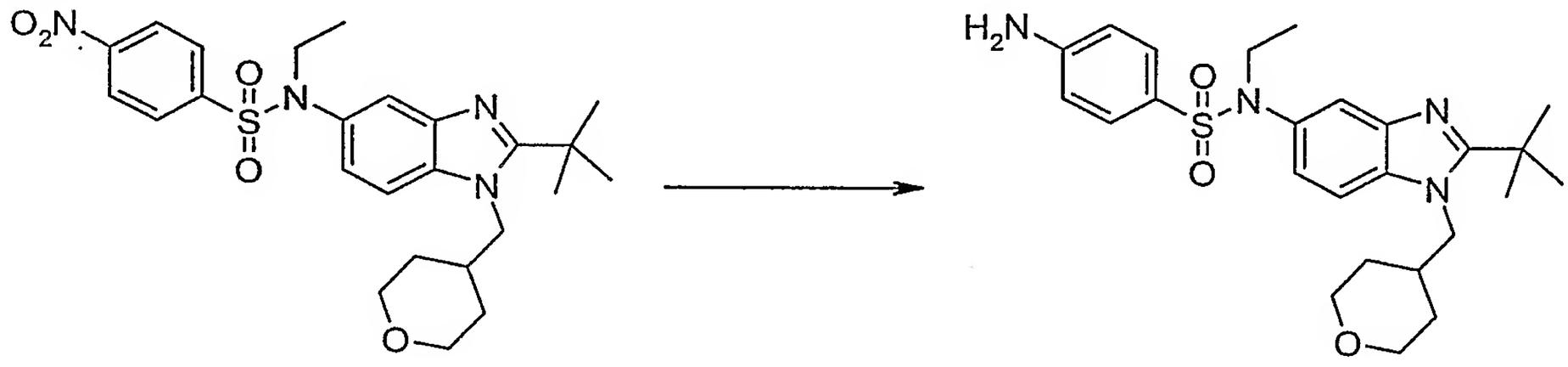
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylacetamide (648.3 mg, 2.06 mmol) was dissolved in 15 mL of EtOH-2*N* HCl (3:2), and then heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3h. After concentration and dried *in vacuo*, 754.71 mg (100%) of a grey white solid was obtained as the title product. MS (ESI) $(M+H)^+ = 316.3$.

Step G: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-nitrobenzenesulfonamide



4-Nitrobenzenesulfonyl chloride (445.9 mg, 2.01 mmol) was added to a solution of 2-*tert*-butyl-*N*-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine hydrochloride (354.1 mg, 1.01 mmol) and DMAP (491.7 mg, 4.03 mmol) in MeCN (20 mL). The reaction mixture was stirred overnight at room temperature, diluted with EtOAc (100 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. The crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 399.6 mg (80%) of a yellow solid as the title compound. MS (ESI) $(M+H)^+ = 501.0$.

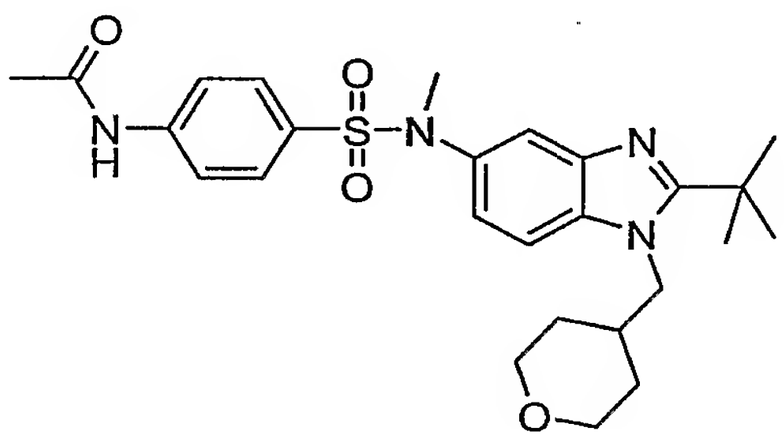
Step H: 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethylbenzenesulfonamide



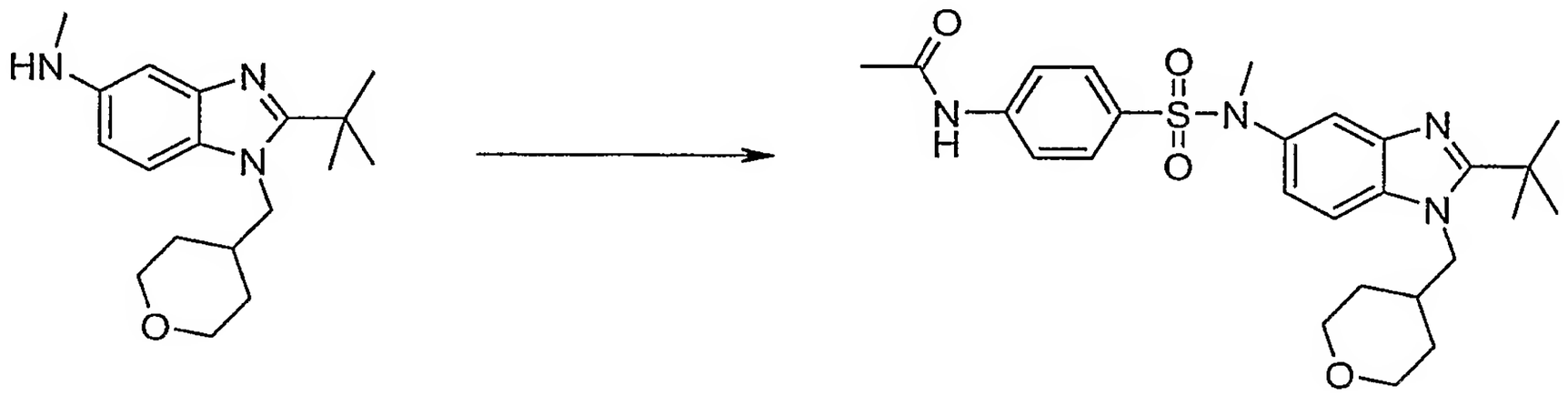
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-ethyl-4-nitrobenzenesulfonamide (399.6 mg, 0.798 mmol) was hydrogenated in ethyl acetate (50 mL) catalyzed by 10% Pd/C (100 mg) at 30-40 psi H_2 in Parr shaker for 6 h at room temperature. After filtration through celite and concentration, 457.9 mg (100%) of a white solid was obtained. Small amounts of the crude product was purified by reversed-phase HPLC using 20-50% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.04 (t, J=7.13 Hz, 3 H), 1.49 - 1.65 (m, 4 H), 1.68 (s, 9 H), 2.25 - 2.55 (m, 1 H,) 3.32 - 3.43 (m, 2 H), 3.66 (q, J=7.03 Hz, 2 H), 3.88 - 4.04 (m, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 6.50 - 6.69 (m, 2 H), 7.19 - 7.26 (m, 2 H), 7.28 (dd, J=8.98, 1.95 Hz, 1 H), 7.50 (d, J=1.76 Hz, 1 H), 7.90 (d, J=8.98 Hz, 1 H). MS (ESI) $(M+H)^+ = 471.0$. Anal. Calcd for $C_{25}H_{34}N_4O_3S$+ 1.80 TFA+0.30 H_2O (681.29): C, 50.42; H, 5.39; N, 8.22; Found: C, 50.38 ; H, 5.21; N, 8.44.

Example 19

N-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide

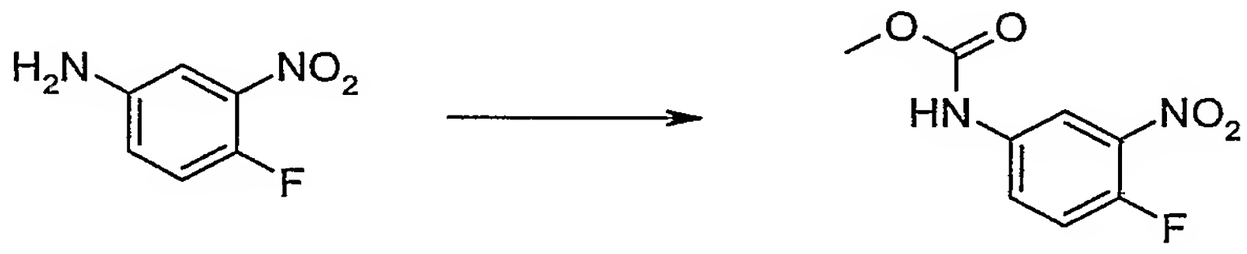


Step A: *N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (for preparation see following steps B to F) (200 mg, 0.663 mmol) and DMAP (16 mg, 0.132 mmol) were dissolved in 10 mL of DCM. N-Acetylsulfanilyl chloride (186 mg, 0.796 mmol) was added and the solution was stirred at rt for 48h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 353 mg (87%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.51 - 1.57 (m, 2 H), 1.56 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.14 (s, 3 H), 2.32 - 2.41 (m, 1 H), 3.25 (s, 3 H), 3.35 (td, J=11.47, 2.64 Hz, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.52 (d, J=7.62 Hz, 2 H), 7.32 (dd, J=8.98, 2.15 Hz, 1 H), 7.45 (d, J=8.98 Hz, 2 H), 7.54 (d, J=1.56 Hz, 1 H), 7.71 (d, J=8.98 Hz, 2 H), 7.88 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 499.0; Anal. Calcd for $C_{26}H_{34}N_4O_4S$ + 1.5 TFA + 0.1 H_2O: C, 51.87; H, 5.36; N, 8.34. Found: C, 51.91; H, 5.28; N, 8.26.

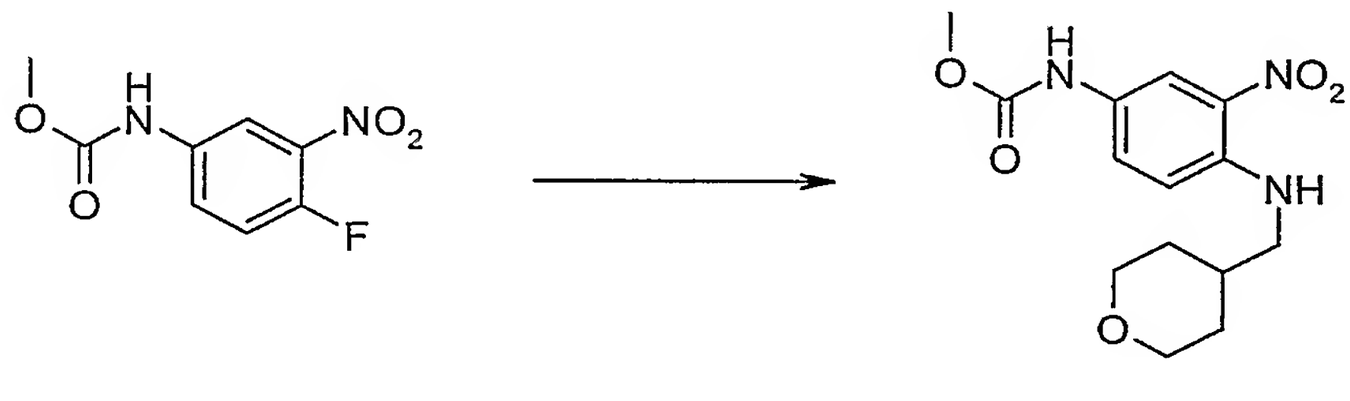
Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate



Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the

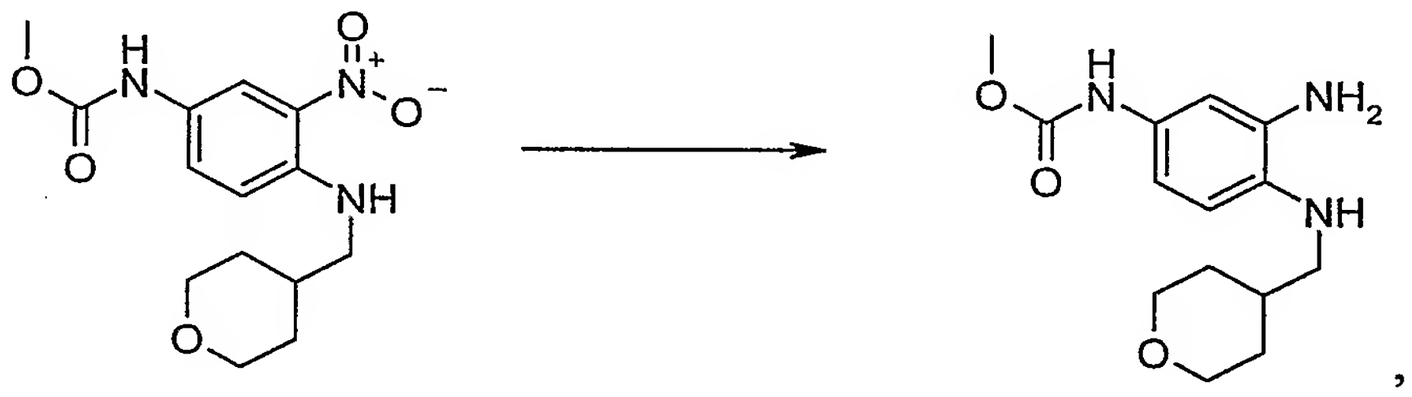
product was directly used for next step without further purification. Yield: 35.5 g (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59Hz, 1H), 8.17 (dd, J = 6.35, 2.64Hz, 1H).

Step C: Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53g (88%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.42 (m, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, *J*=6.74, 5.57 Hz, 2 H), 3.42 (td, *J*=11.86, 2.05 Hz, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

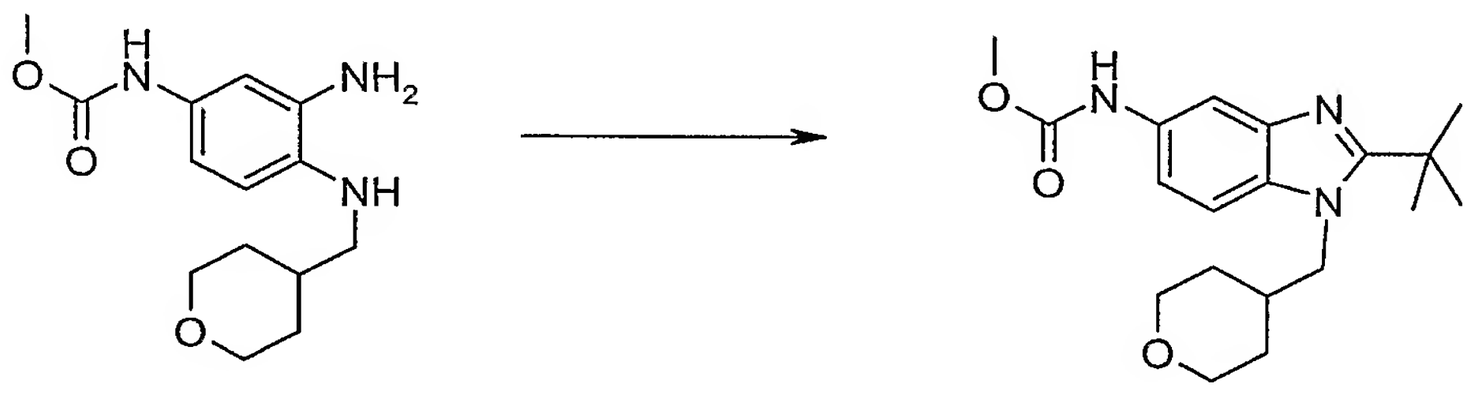
Step D: Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount

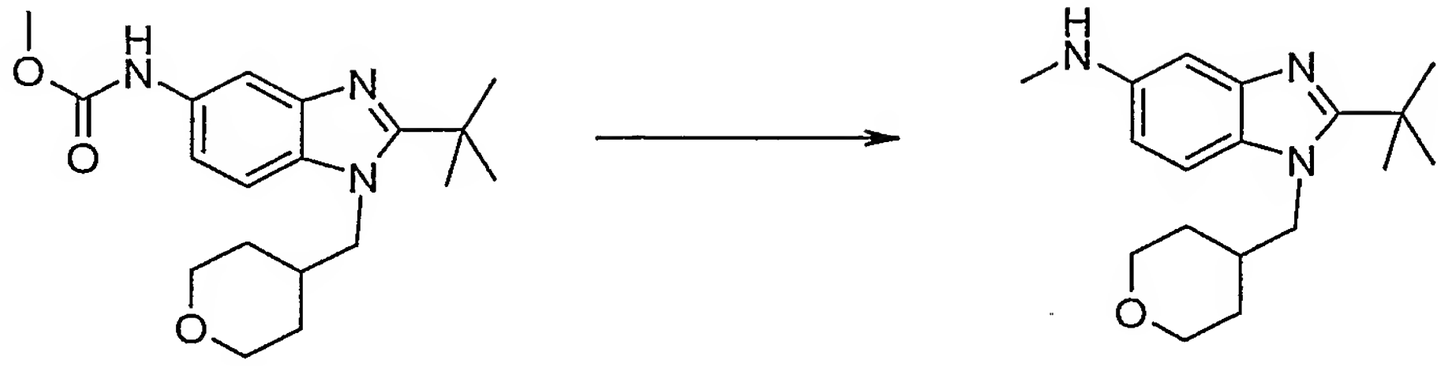
of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29g (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.40 (m, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (dt, *J*=11.81, 2.15 Hz, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

Step E: Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate (2.29g, 8.20 mmol) and DMAP (0.20g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 25 mL of AcOH and heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81g (64%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, *J*=2.93 Hz, 1 H) 3.99 (t, *J*=3.03 Hz, 1 H) 4.18 (d, *J*=7.42 Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, *J*=1.95 Hz, 1 H).

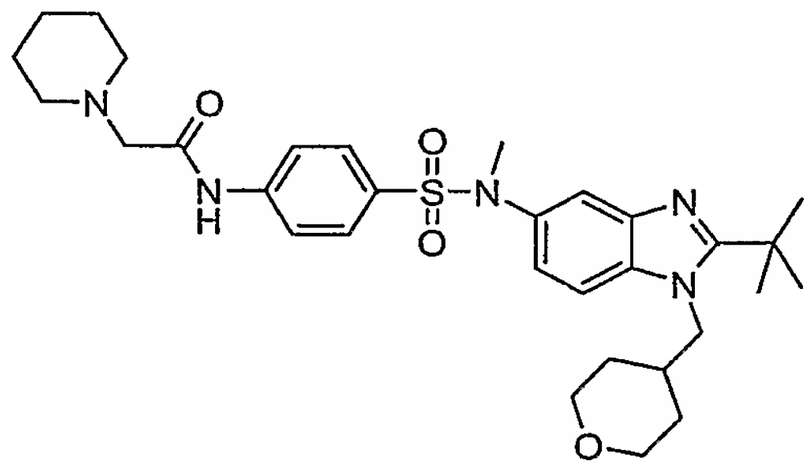
Step F: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



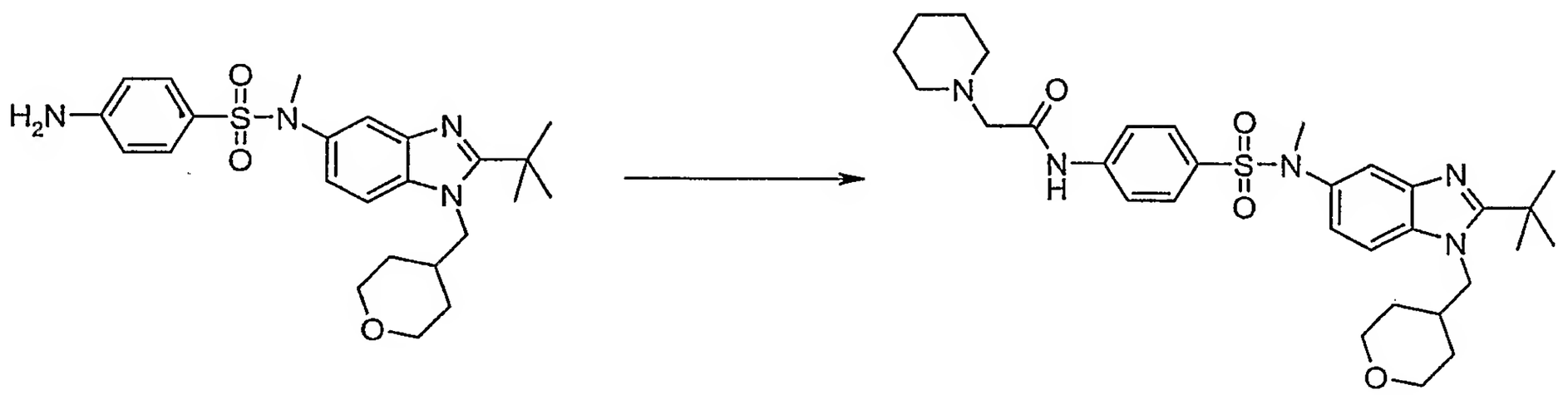
Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80g, 5.21 mmol) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min. Anhydrous Na_2SO_4 (10g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 1.54g (98%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

Example 20

***N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-piperidin-1-ylacetamide**

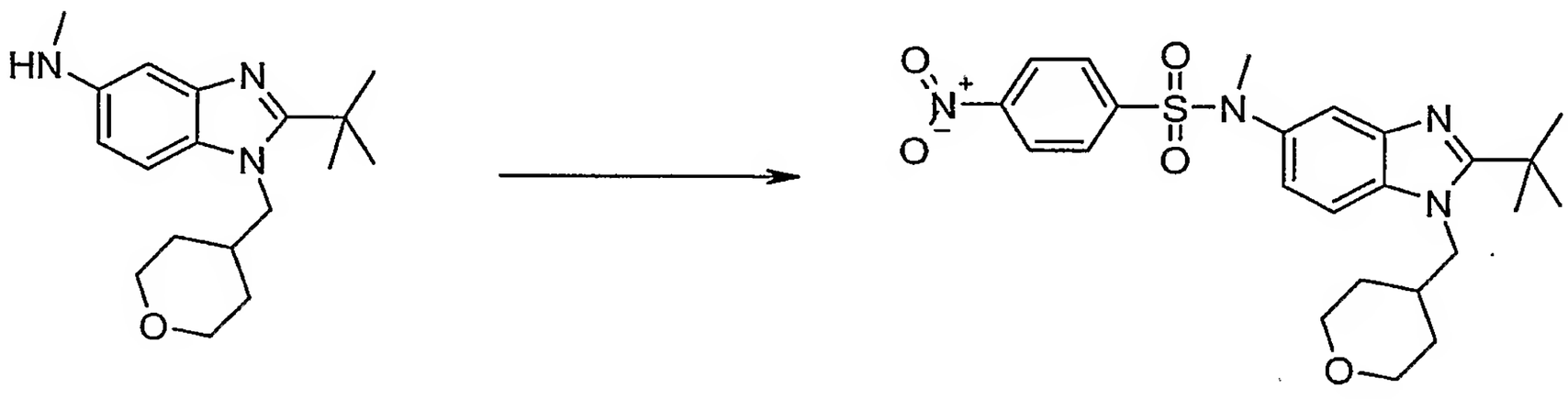


Step A: *N*-(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-piperidin-1-ylacetamide



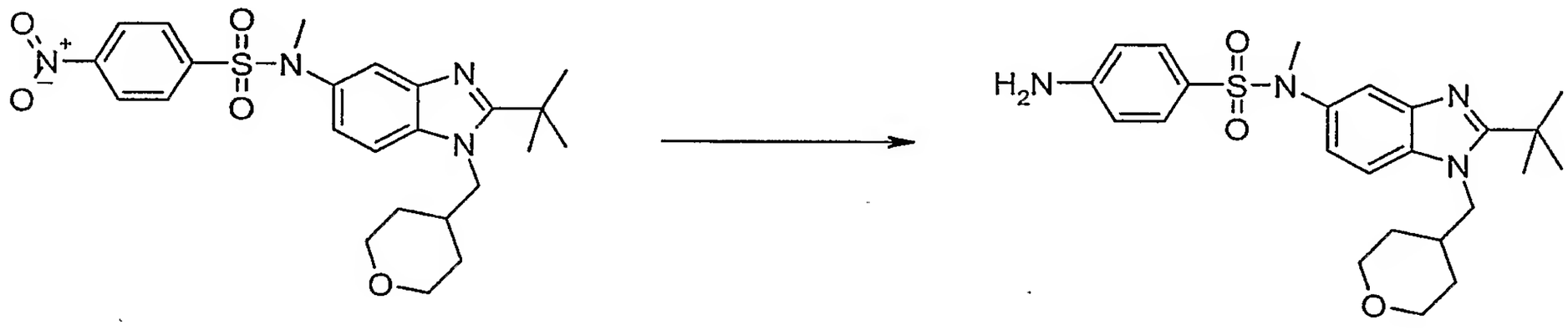
4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (for preparation see following steps B and C) (80 mg, 0.0175 mmol) and bromoacetyl chloride (0.036 mL, 0.0438 mmol) were stirred in 3 mL of DCE containing a catalytic amount of DMAP at rt for 3h. Piperidine (0.086 mL, 0.0875 mmol) was added and the solution was heated at 125°C for 15 min using a Personal Chemistry microwaves instrument. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 76 mg (62%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.40 - 1.45 (m, 3 H), 1.44 - 1.52 (m, 2 H), 1.57 (s, 9 H), 1.71 - 1.80 (m, 3 H), 1.80 - 1.87 (m, 2 H), 2.21 - 2.28 (m, 1 H), 2.98 (t, *J*=11.01 Hz, 2 H), 3.15 (s, 3 H), 3.24 (t, *J*=11.39 Hz, 2 H), 3.50 (m, 2 H), 3.83 (d, *J*=3.84 Hz, 1 H), 3.85 (d, *J*=3.33 Hz, 1 H), 4.01 (s, 2 H), 4.41 (d, *J*=7.42 Hz, 2 H), 7.18 (d, *J*=8.96 Hz, 1 H), 7.40 (d, *J*=8.70 Hz, 2 H), 7.49 (s, 1 H), 7.65 (d, *J*=8.70 Hz, 2 H), 7.76 (d, *J*=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 582.0.

Step B: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (60 mg, 0.199 mmol) and p-nitrophenylsulfonyl chloride (57 mg, 0.259 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes :EtOAc as eluent. Yield: 89 mg (92%). ^1H NMR (400 MHz, CHLOROFORM-D) δ 1.50 - 1.60 (m, 13 H), 2.24 - 2.35 (m, 1 H), 3.27 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=2.83 Hz, 1 H), 4.02 (t, *J*=2.93 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.19 - 7.23 (m, 2 H), 7.28 - 7.35 (m, 1 H), 7.77 (d, *J*=8.79 Hz, 2 H), 8.30 (d, *J*=8.98 Hz, 2 H).

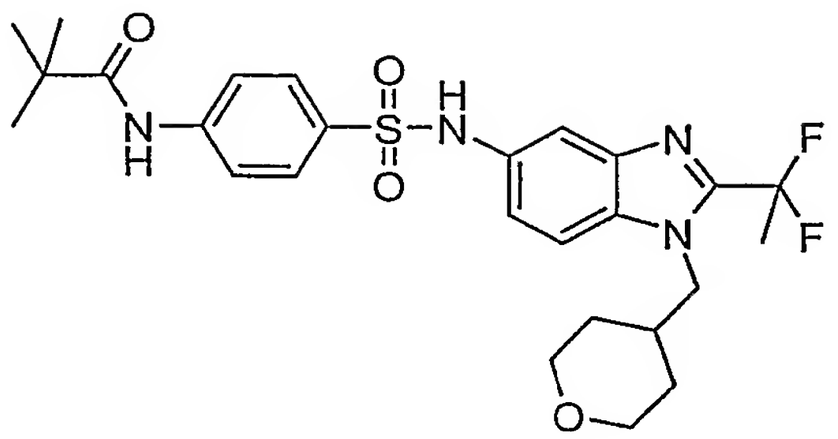
Step C: 4-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



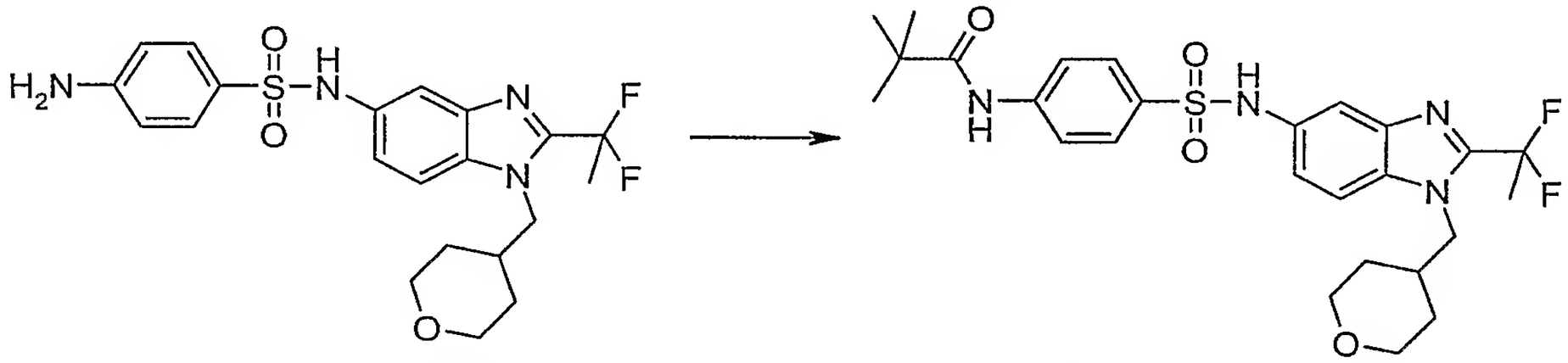
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (85 mg, 0.175 mmol) was dissolved in 20 mL of 1:1 / EtOH : EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) at rt for 12h in a Parr hydrogenation apparatus. The solution was filtered through celite and the solvent was evaporated. Yield: 80 mg (99%). MS (ESI) $(M+H)^+$ 457.6.

Example 20

***N*-[4-({[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2,2-dimethylpropanamide**

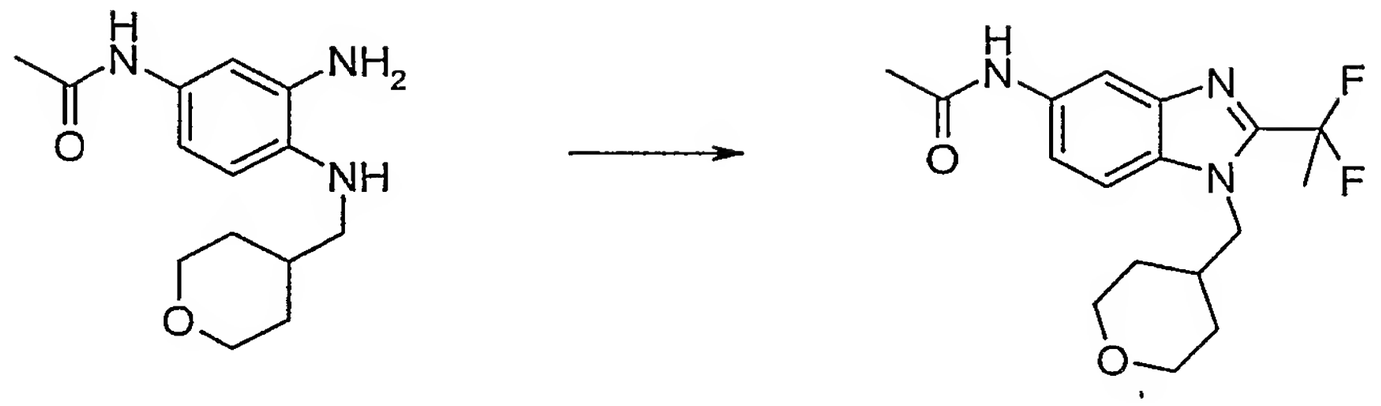


Step A: *N*-[4-({[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)phenyl]-2,2-dimethylpropanamide



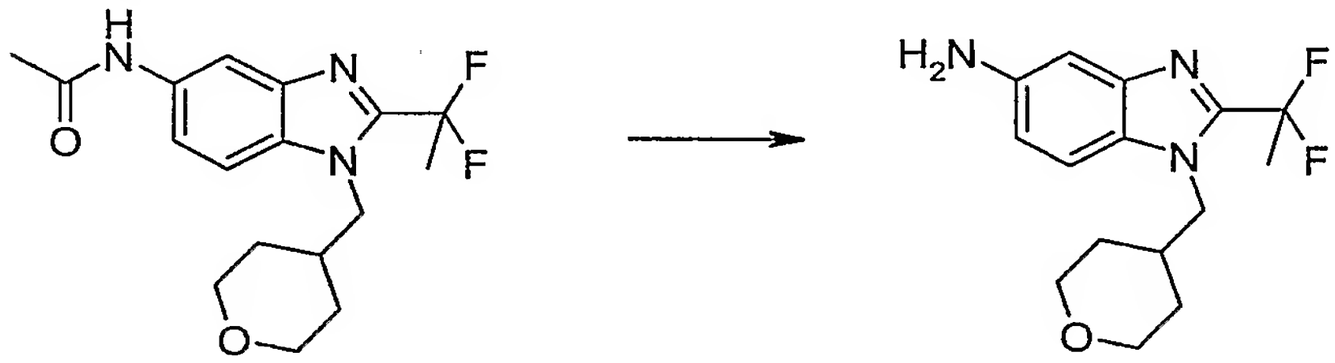
2,2-Dimethylpropanoyl chloride (30 μL, 0.24 mmol) was added to a solution of 4-amino-*N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (100 mg, 0.22 mmol) (for preparation, see the following steps B to E) and Et_3N (37 μL, 0.26 mmol) in DCE (12 mL). The reaction mixture was stirred overnight and the solvent was concentrated. The product was purified by reverse-phase preparative HPLC using MeCN 10 to 90% gradient in water to provide the TFA salt of the title compound as white solid. Yield: 105 mg (88%); ^{1}H NMR (600 MHz, CD_3OD) δ 1.25 (s, 9 H), 1.35 - 1.48 (m, 5 H), 2.19 (t, J=19.20 Hz, 3 H), 2.23 - 2.29 (m, 1 H), 3.89 (dd, J=10.88, 3.20 Hz, 2 H), 4.28 (d, J=7.68 Hz, 2 H), 7.18 (dd, J=8.83, 1.92 Hz, 1 H), 7.41 (d, J=1.79 Hz, 1 H), 7.55 (d, J=8.96 Hz, 1 H), 7.59 - 7.70 (m, 4 H); MS (ESI) $(M+H)^+$ 535.0; Anal. Calcd for $C_{26}H_{32}F_2N_4O_4S$ + 0.2 TFA + 0.8 H_2O + 0.1 MeCN: C, 55.47; H, 5.97; N, 9.97. Found: C, 55.42; H, 6.02; N, 9.90.

Step B: *N*-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide



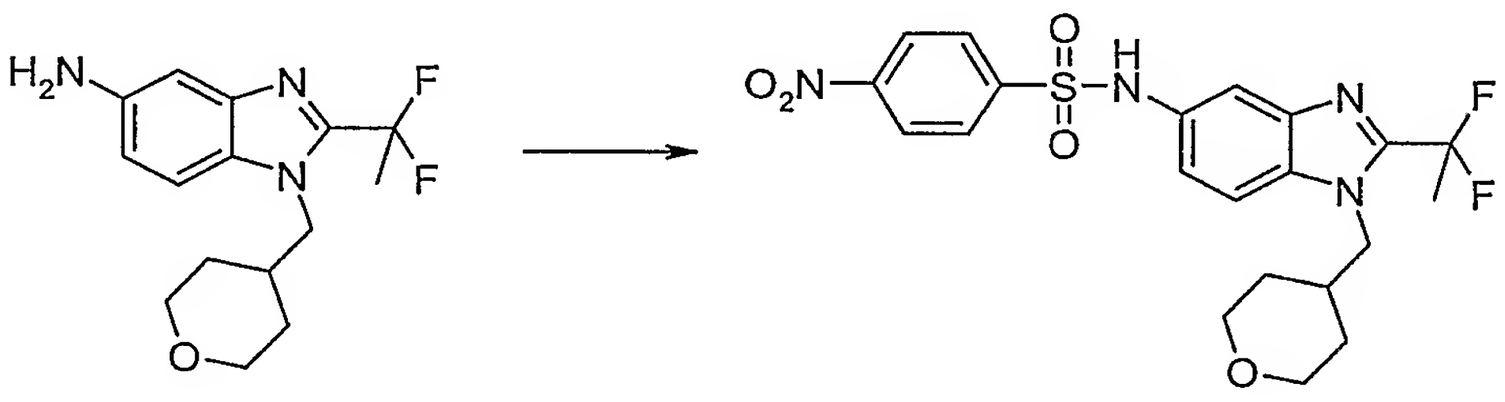
HATU (1.58 g, 4.17 mmol) and *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (1.00 g, 3.79 mmol) were added to a solution of 2,2-difluoropropanoic acid (0.43 g, 3.98 mmol) and DIPEA (0.80 mL, 4.55 mmol) in DMF (100 mL) at ambient temperature. The reaction mixture was stirred overnight and the solvent was concentrated. The intermediate was heated to 80°C for 3 hrs in glacial AcOH (100 mL), and the solvent was concentrated. The crude product was recovered in DCM (300 mL), washed with saturated $NaHCO_3$ solution (3 x 100 mL), brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was purified by normal-phase MPLC using MeOH 5% and Acetone 10% in DCM to provide the title compound as a white solid. Yield: 1.07 g (83%); MS (ESI) $(M+H)^+$ 338.2.

Step C: 2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



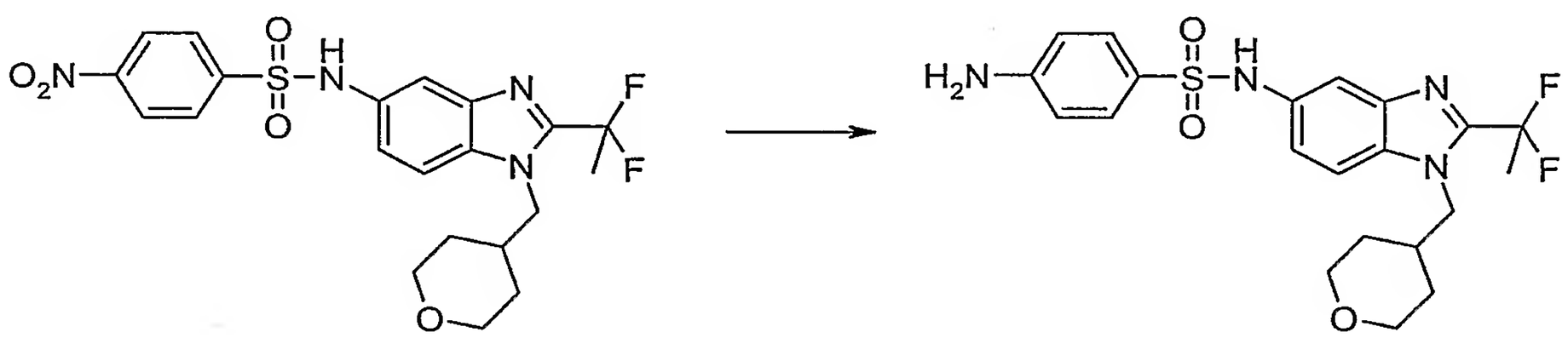
A mixture of *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (1070 mg, 3.17 mmol), 6 M aquesous solution of NaOH (5 mL) and MeOH (5 mL) was heated to 70°C for 24 hrs. The reaction mixture was diluted with water (200 mL) and the product was extracted with EtOAc (4 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was concentrated to provide the title compound as white solid. Yield: 900 mg (96%); MS (ESI) $(M+H)^+$ 296.2.

Step D: *N*-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide



4-Nitrobenzenesulfonyl chloride (562 mg, 2.53 mmol) was added to a solution of 2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (500 mg, 1.69 mmol) and DMAP (413 mg, 3.38 mmol) in DCE (40 mL) at 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1hr. The solvent was concentrated and the product was purified on silica gel by MPLC using EtOAc 20% to 90% in heptane to provide the title compound as white solid. Yield: 378 mg (47%); MS (ESI) $(M+H)^+$ 481.3.

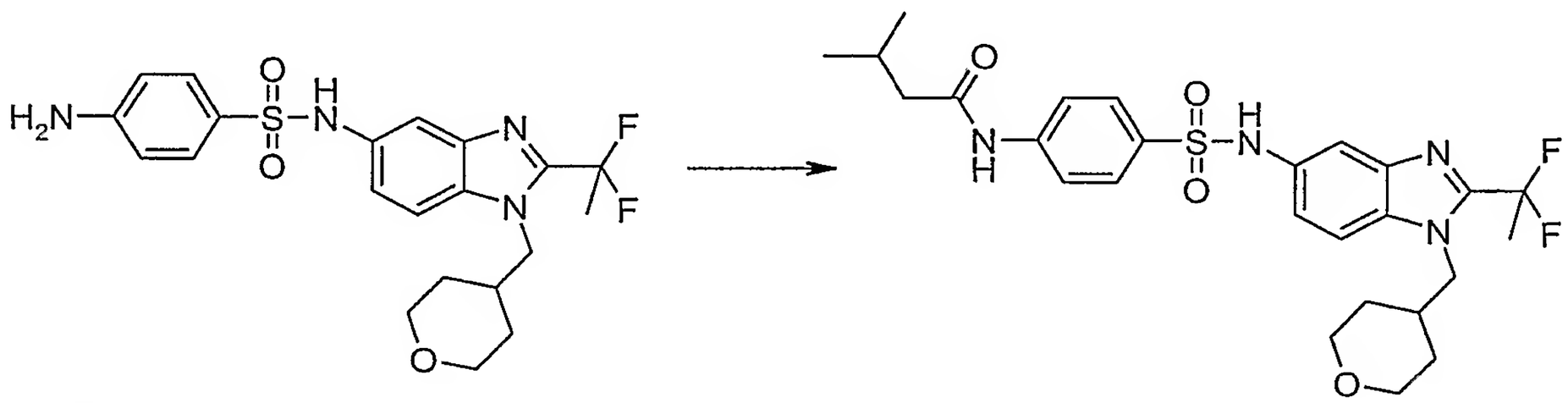
Step E: 4-Amino-*N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide



A mixture of *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-nitrobenzenesulfonamide (378 mg, 0.78 mmol), Pd/C 10% (catalytic amount) and EtOAc (50 mL) was shaken overnight in a Parr® hydrogenation apparatus under 40 PSI of hydrogen. The reaction mixture was filtered over a celite pad and the solvent was concentrated to provide the title compound as white solid. Yield: 365 mg (99%). MS (ESI) $(M+H)^+$ 451.3.

Example 21

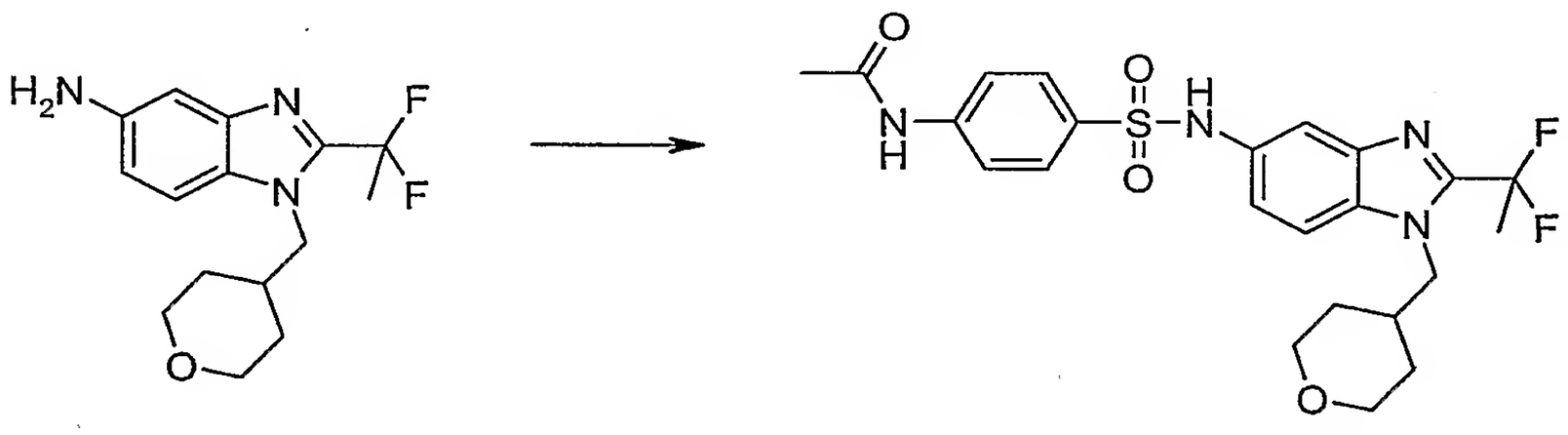
_N_-[4-({[2-(1,1-Difluoroethyl)-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-yl]amino}sulfonyl)phenyl]-3-methylbutanamide



Following step A of Example 20, using 3-methylbutanoic acid (29 mg, 0.24 mmol), provided the TFA salt of the title compound as white solid. Yield: 110 mg (92%); ^{1}H NMR (600 MHz, CD_3OD) δ 0.96 (d, J=6.40 Hz, 6 H), 1.36 - 1.49 (m, 4 H), 2.06 - 2.16 (m, 2 H), 2.17 - 2.23 (m, 4 H), 2.23 - 2.28 (m, 1 H), 3.26 - 3.35 (m, 2 H), 3.84 - 3.93 (m, 2 H), 4.28 (d, J=7.42 Hz, 2 H), 7.19 (dd, J=8.83, 1.92 Hz, 1 H), 7.42 (d, J=1.79 Hz, 1 H), 7.56 (d, J=8.71 Hz, 1 H), 7.63 (s, 4 H); MS (ESI) $(M+H)^+$ 535.0; Anal. Calcd for $C_{26}H_{32}N_4O_4S$ + 0.9 TFA + 0.7 H_2O: C, 51.38; H, 5.32; N, 8.62. Found: C, 51.44; H, 5.34; N, 8.53.

Example 22

_N_-[4-({[2-(1,1-Difluoroethyl)-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-yl]amino}sulfonyl)phenyl]acetamide

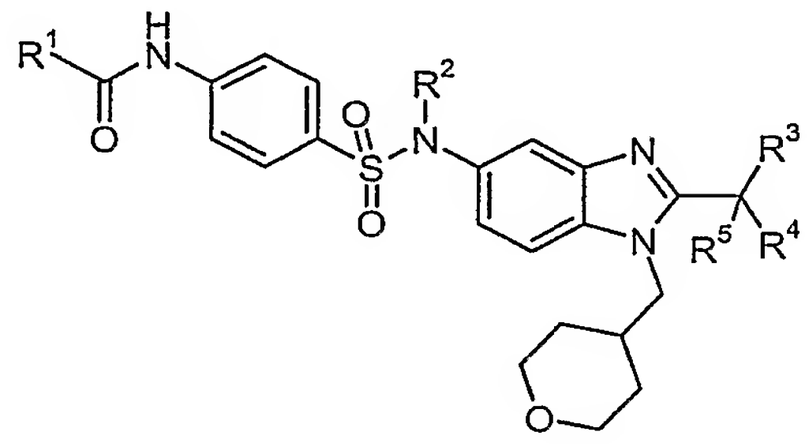


4-(Acetylamino)benzenesulfonyl chloride (66 mg, 0.28 mmol) was added to solution of 2-(1,1-difluoroethyl)-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-amine (70 mg, 0.23 mmol) and DMAP (58 mg, 0.47 mmol) in MeCN at 70°C. The reaction mixture was stirred for 1 hr. and the solvent was concentrated. The product was purified by reverse-phase preparative HPLC using MeCN 10 to 90% gradient in water to provide the TFA salt of the title compound as a white solid. Yield: 43 mg (30%); ^{1}H NMR (600 MHz, CD_3OD) δ 1.35 - 1.48 (m, 5 H), 2.06 - 2.13 (m, 3 H),

2.19 (t, J=19.46 Hz, 3 H), 3.90 (d, J=9.47 Hz, 2 H), 4.28 (d, J=7.68 Hz, 2 H), 7.18 (d, J=6.40 Hz, 1 H), 7.41 (s, 1 H), 7.55 (d, J=7.42 Hz, 1 H), 7.59 - 7.67 (m, 6 H); MS (ESI) $(M+H)^+$ 493.0.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 isselected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

2. A compound as claimed in claim 1, wherein

R^1 is selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2,2-dimethyl-1-propyl, cyclopropyl and cyclobutyl;

R^2 isselected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

3. A compound as claimed in claim 1,

wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are methyl.

4. A compound as claimed in claim 1, wherein

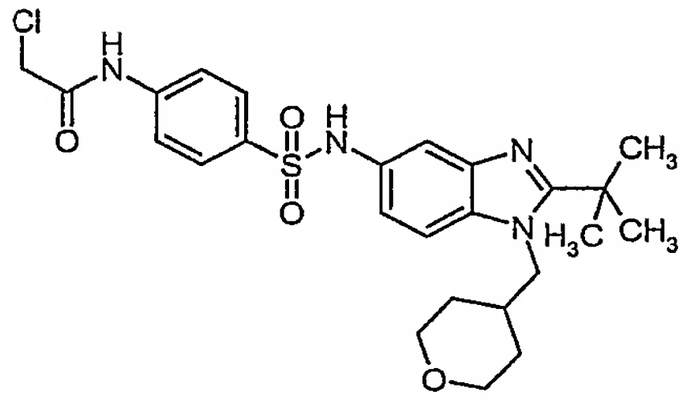
R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 isselected from –H and methyl;

R^3 is methyl; and

R^4 and R^5 are fluoro.

5. A compound selected from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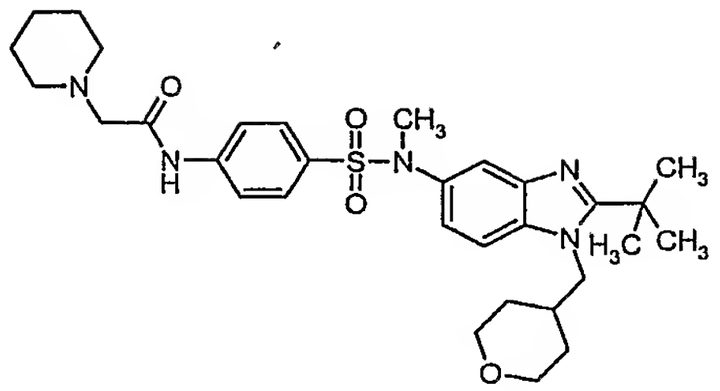
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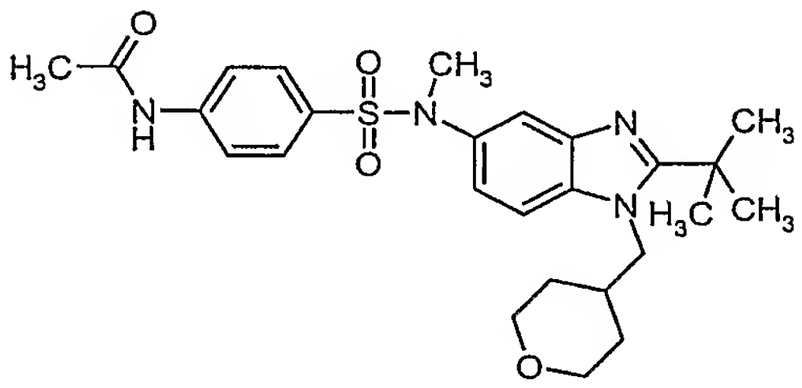
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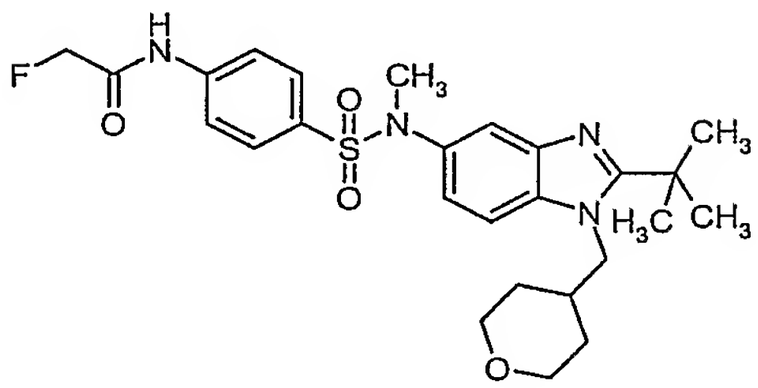
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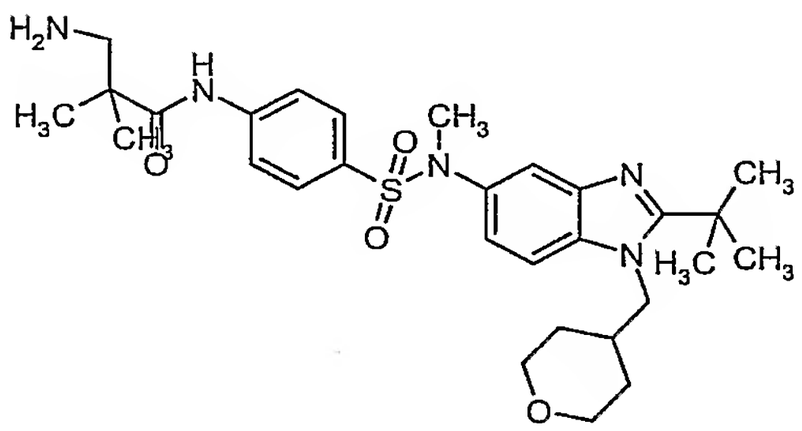
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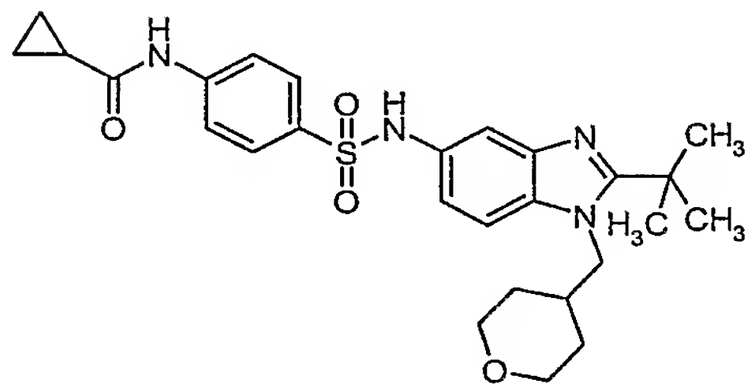
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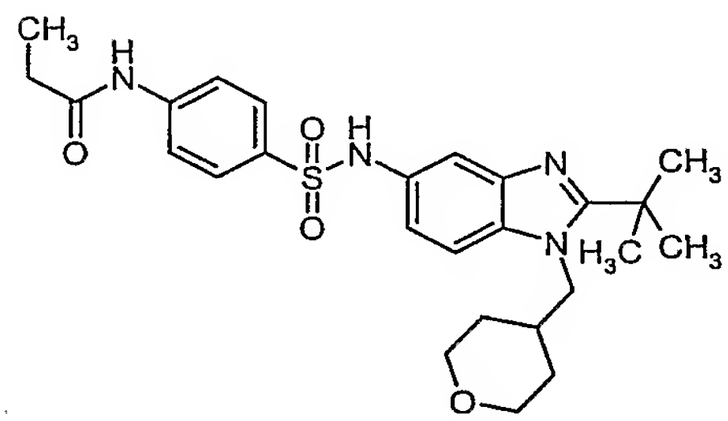
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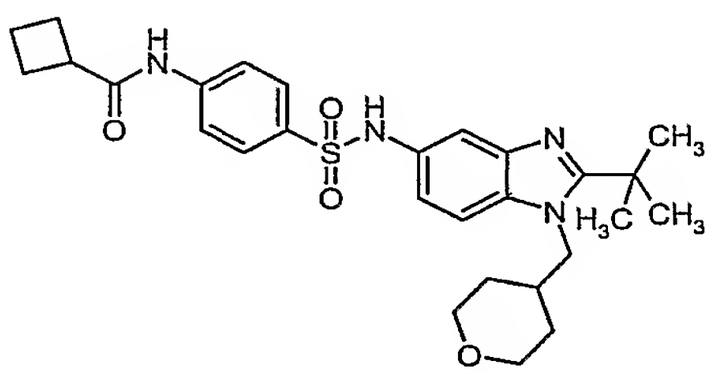
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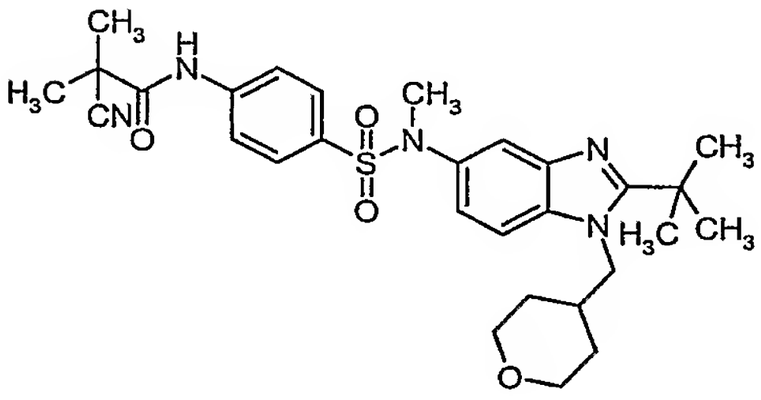
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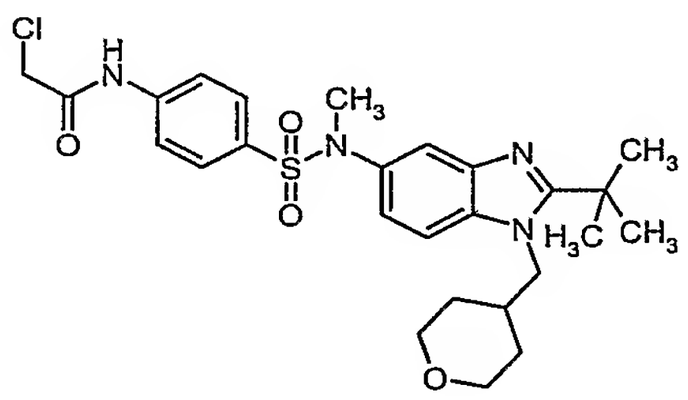
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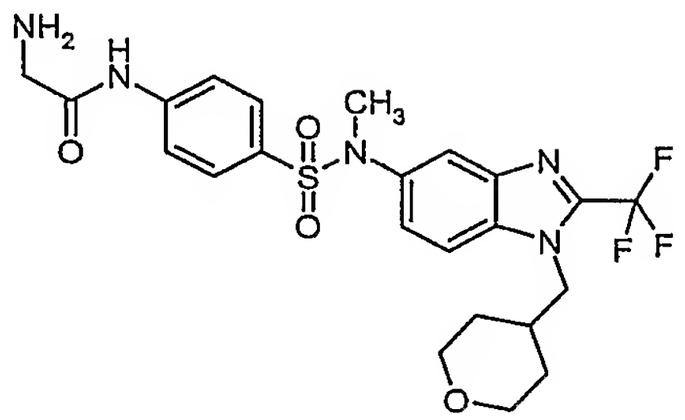
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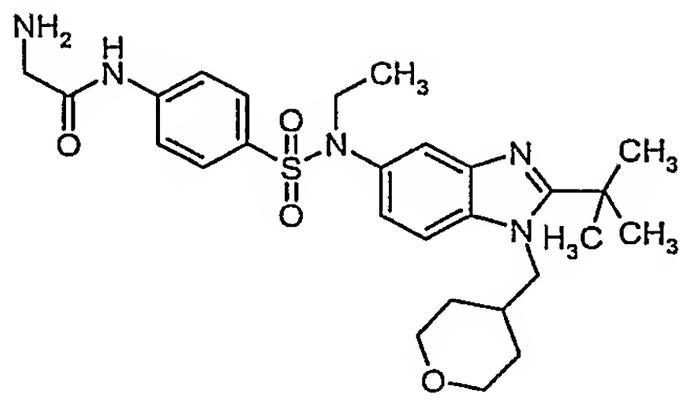
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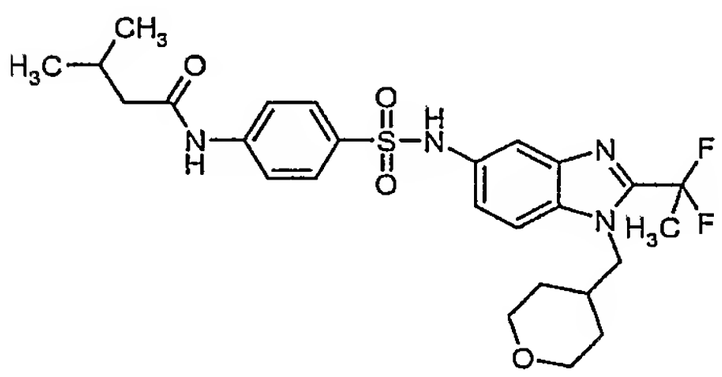
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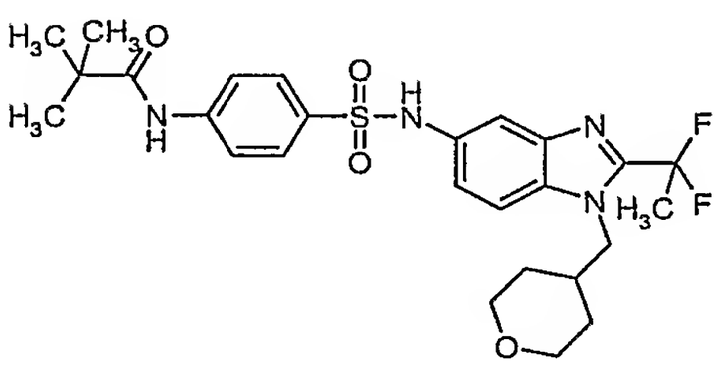
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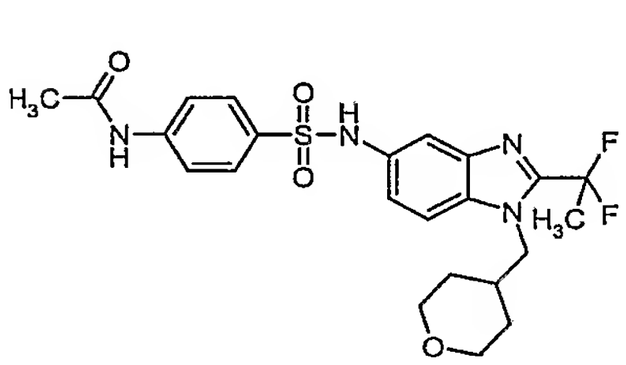
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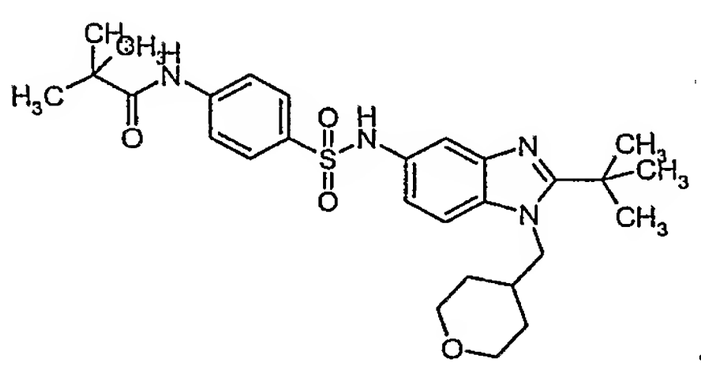
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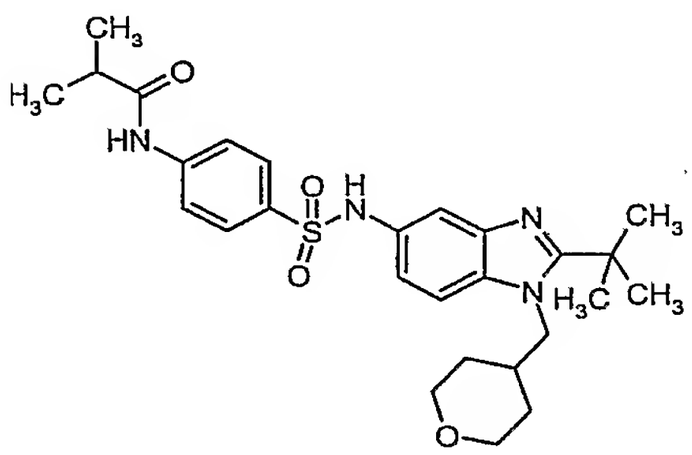
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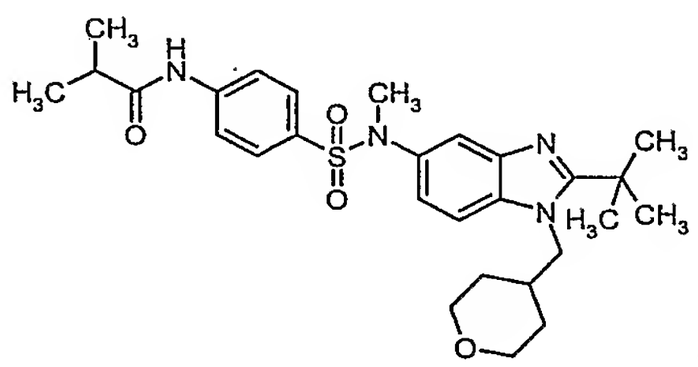
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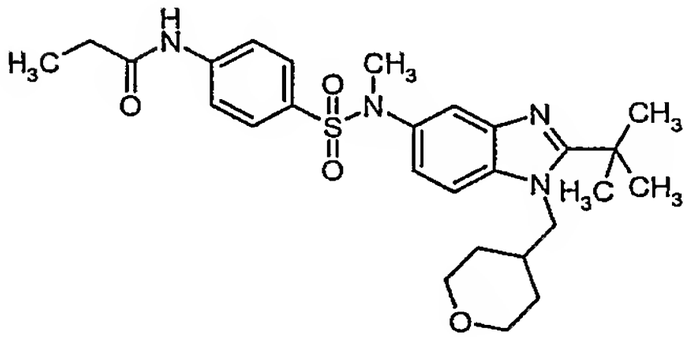
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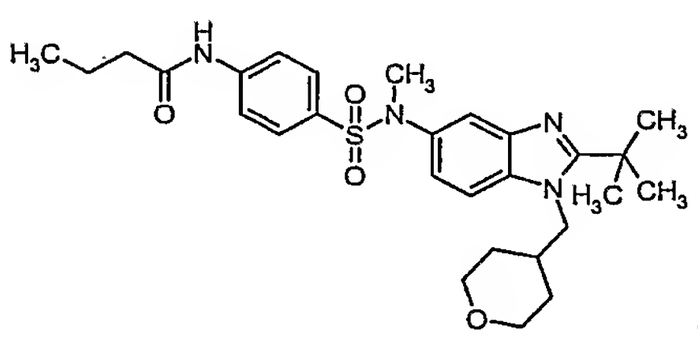
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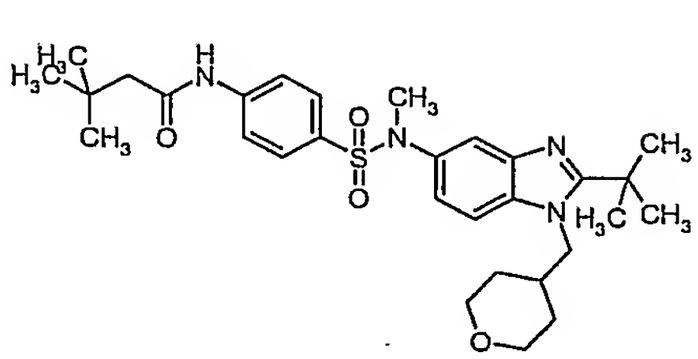
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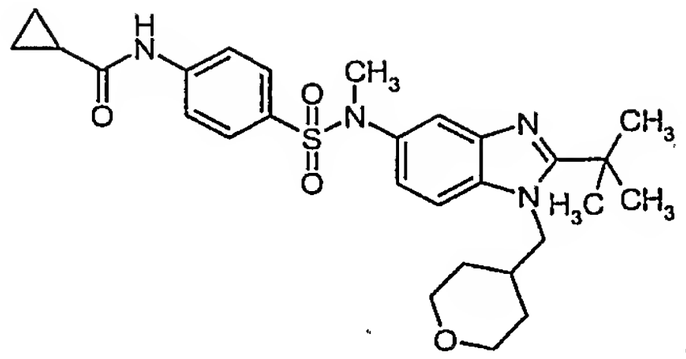
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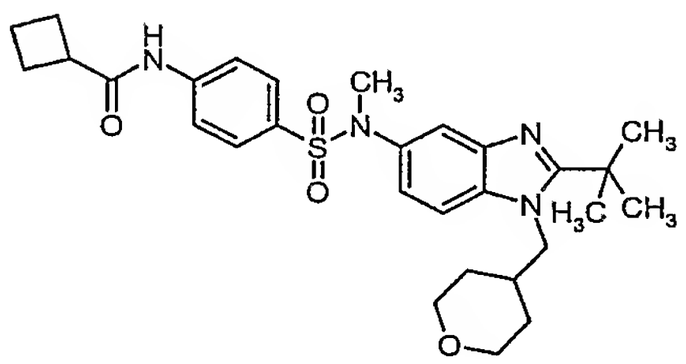
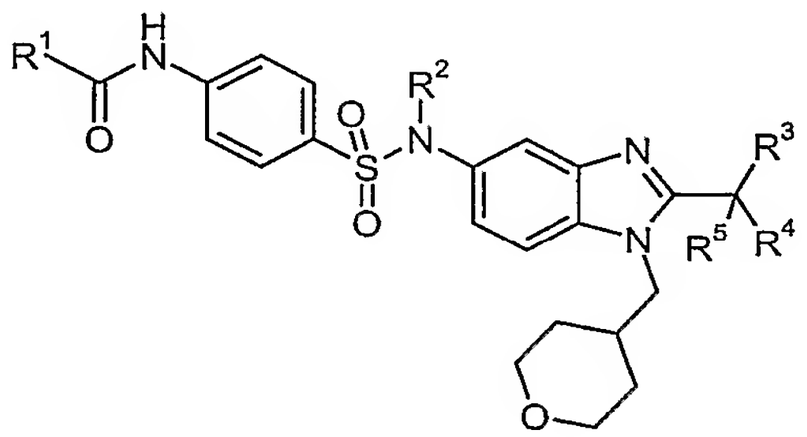

, and pharmaceutically acceptable salts thereof.

6. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl, wherein said C_{1-6}alkyl, and C_{3-6}cycloalkyl are optionally substituted by one or more groups selected from amino, cyano, halogen, and C_{2-5}heterocycloalkyl;

R^2 isselected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

7. A compound according to any one of claims 1-6 for use as a medicament.

8. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the therapy of pain.

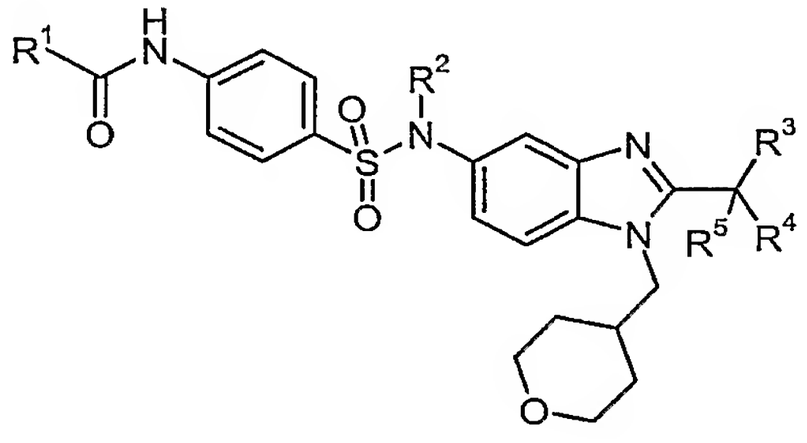
9. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of anxiety disorders.

10. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-6 and a pharmaceutically acceptable carrier.

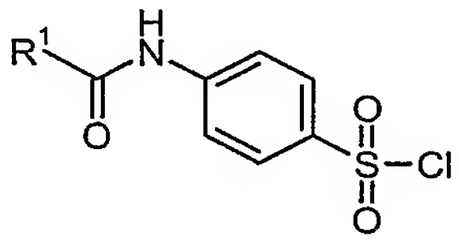
12. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-6.

13. A method for preparing a compound of Formula I, comprising:

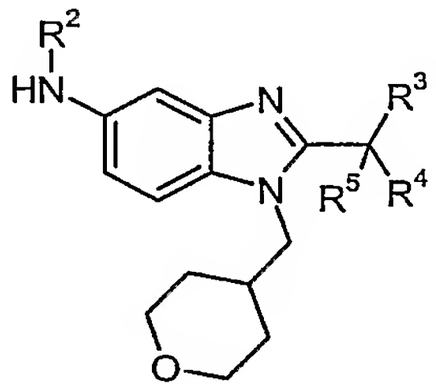


I

reacting a compound of Formula II with a compound of formula III,



II



III

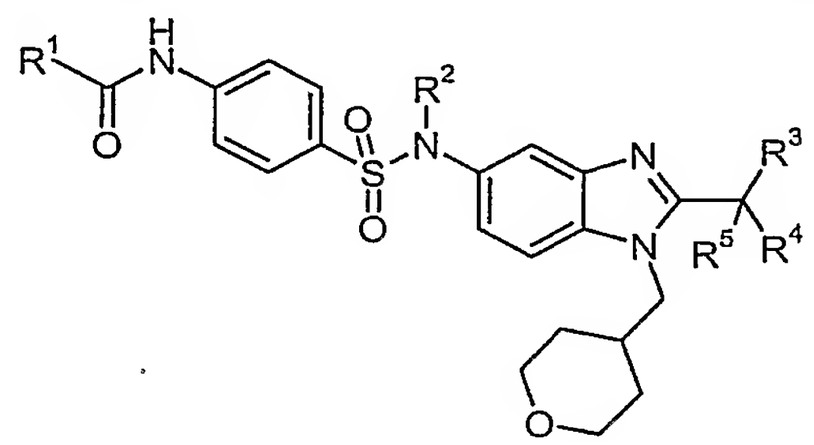
wherein

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl;

R^2 isselected from –H and methyl; and

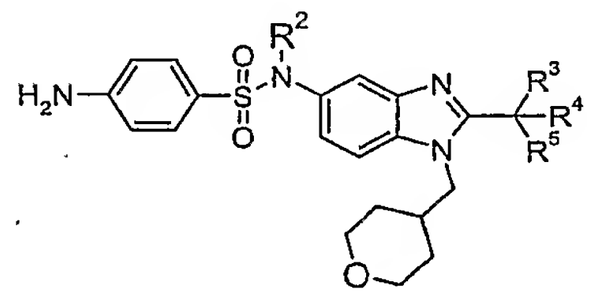
R^3, R^4 and R^5 are independently selected from fluoro and methyl.

14. A mthod for preparing a compound of Formula I, comprising:



I

reacting a compound of Formula IV with R^1-C(=O)-X,



IV

wherein

X is selected from –Cl, -Br and –I;

R^1 is selected from C_{1-6}alkyl, and C_{3-6}cycloalkyl which are optionally substituted by amino, cyano, halogen, and C_{2-5}heterocycloalkyl;

R^2 is selected from –H and methyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001401

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005030733 A1 (ASTRAZENECA UK LIMITED), 7 April 2005 (07.04.2005) --	1-14
P,X	WO 2005030761 A1 (ASTRAZENECA AB ET AL), 7 April 2005 (07.04.2005) --	1-14
P,A	WO 2004108712 A1 (ASTRAZENECA AB), 16 December 2004 (16.12.2004) --	1-14
A	WO 02085866 A1 (ASTRAZENECA AB), 31 October 2002 (31.10.2002) -- --------	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2005	07 -12- 2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EK Telephone No. +46 8 782 25 00

Continuation of cover sheet

C07D 405/06 (2006.01)
A61K 31/4184 (2006.01)
A61K 31/454 (2006.01)
A61P 1/00 (2006.01)
A61P 25/00 (2006.01)
A61P 25/16 (2006.01)
A61P 25/22 (2006.01)
A61P 25/28 (2006.01)
A61P 35/00 (2006.01)
A61P 9/00 (2006.01)
C07D 405/14 (2006.01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001401

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 12 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/11/2005

International application No.
PCT/SE 2005/001401

WO	2005030733	A1	07/04/2005	SE	0302571 D	00/00/0000
WO	2005030761	A1	07/04/2005	SE	0302570 D	00/00/0000
WO	2004108712	A1	16/12/2004	AU	2003280905 A	00/00/0000
				EP	1579119 A	28/09/2005
				SE	0301701 D	00/00/0000
WO	02085866	A1	31/10/2002	AU	7477201 A	14/01/2002
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				CA	2414995 A	10/01/2002
				CA	2444381 A	31/10/2002
				CN	1503787 A	09/06/2004
				CZ	20032833 A	12/05/2004
				EE	200300524 A	16/02/2004
				EP	1307481 A	07/05/2003
				EP	1390350 A	25/02/2004
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				JP	2004502416 T	29/01/2004
				JP	2004528334 T	16/09/2004
				MX	PA03009558 A	12/02/2004
				NO	20034665 A	10/12/2003
				NZ	528403 A	27/05/2005
				PL	366517 A	07/02/2005
				SE	0101387 D	00/00/0000
				SK	13032003 A	03/01/2005
				US	20040116465 A	17/06/2004
				ZA	200307752 A	03/01/2005